IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIODELIVERY SCIENCES INTERNATIONAL, INC. and ARIUS TWO, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 18-1395 (CFC) (CJB)
ALVOGEN PB RESEARCH & DEVELOPMENT LLC, ALVOGEN MALTA OPERATIONS LTD., ALVOGEN PINE BROOK LLC, ALVOGEN, INC., and ALVOGEN GROUP, INC.,	)	
Defendants.	)	

ALVOGEN'S PROPOSED FINDINGS OF FACT

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TABLE OF CONTENTS

I. BACKGROUND

1. The Tapolsky patents are generally directed to a bioerodable mucoadhesive ("BEMA") device that includes (1) a polymeric diffusion environment (or "mucoadhesive layer") containing the drug, at least one film-forming water-erodible adhesive polymer and at least one bioadhesive polymer, and (2) a backing layer (or barrier layer) to provide a "unidirectional gradient" of the drug toward the mucosal surface and prevent the drug from being swallowed. (*See generally* DTX-173, *see also* Tr. 106:17-109:21.)

2. The Tapolsky patents are platform technology useful for many categories of drugs, including opioids. For example, Tapolsky identifies butorphanol as an exemplary opioid for use in the patented BEMA device. (DTX-173 at [0053], *see also* Tr. 112:16-23.)

3. The '866 and '843 patents generally claim a Tapolsky BEMA device containing buprenorphine, wherein the polymeric diffusion environment is buffered to a pH that is optimal for the dissolution, ionization and absorption of buprenorphine. (*See generally* JTX-001, JTX-002, *see also* Tr. 200:21-201:5.)

4. The '539 patent is generally directed to a Tapolsky BEMA device disclosed in Vasisht I, wherein the backing layer is buffered to a pH of 4.0 to 4.8. (*See generally* JTX-003, *see also* Tr. 209:18-210:3.)

II. PERSON OF ORDINARY SKILL IN THE ART

5. A POSA would have a bachelor's degree in pharmaceutical sciences, chemistry or related field, plus three to five years of relevant experience in developing transmucosal dosage forms. Alternatively, a POSA would have a Ph.D. in one of those fields and less practical experience. (Tr. 87:10-25.)

6. At trial, BDSI did not object to this description of a POSA, and, Dr. Robert Williams testified that his opinions on behalf of BDSI would not change in view of this definition of a POSA. (Tr. 88:1-88:14, 721:22-722:4.)

III. THE ASSERTED CLAIMS OF THE '866 PATENT AND '843 PATENT ARE OBVIOUS

A. Scope and Content of the Prior Art[1]

7. Buprenorphine, discovered in 1966, is an opioid analgesic known to treat acute and chronic pain. (DTX-165-0001-0003, 0008-0009; JTX-471-0003; Tr. 96:15-25, 97:19-98:1, 98:13-22.)

8. The history of buprenorphine is generally set forth in the following timeline:

[1] The references in this section all published prior to July 21, 2006, the earliest possible filing date of the '866 and '843 patents. D.I. 249 at 2-5; DTX-173-001; DTX-178-001; DTX-165-001; DTX-077-001; JTX-248-001; JTX-249-001; DTX-174-001; JTX-471-003; DTX-203-001.)

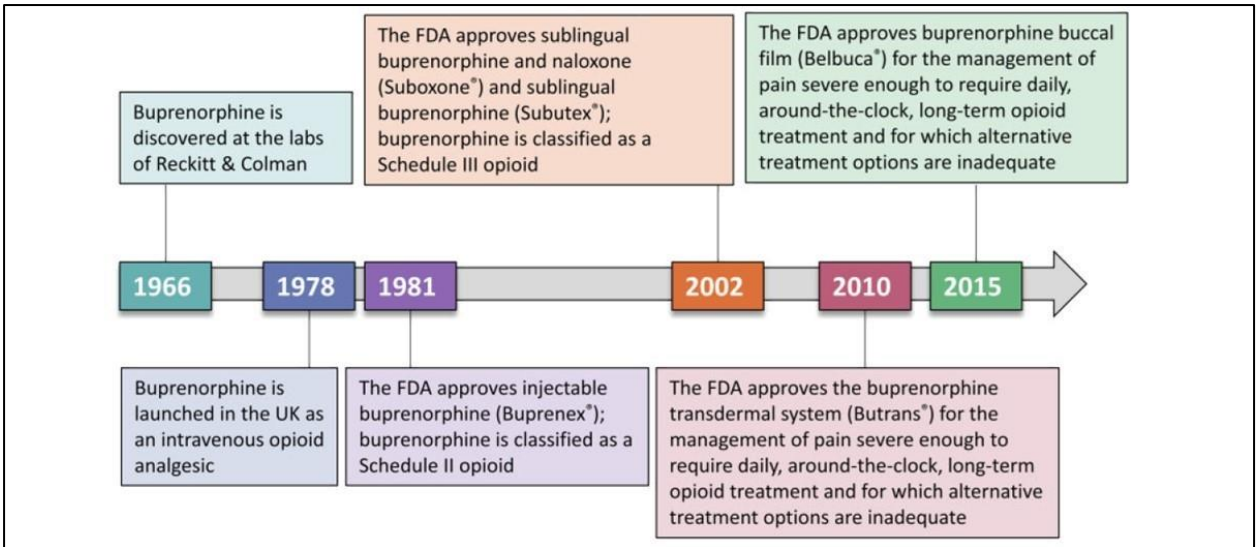


Figure 1. The history of buprenorphine. Buprenorphine was originally developed as an analgesic and was subsequently used for OUD before novel delivery systems allowed for approval in chronic pain management [8,9,12,13]. FDA=Food and Drug Administration; OUD=opioid use disorder.

(DDX1-10; JTX-471-0003; Tr. 480:8-482:19.)

9. POSAs knew buprenorphine to have "high first pass effect," which means that the liver destroys and renders the buprenorphine less effective if swallowed. (DTX-077-0001; JTX-248-0001; DTX-165-0002, 0005; Tr. 91:2-92:13, 94:20-95:3, 97:12-18.)

10. Because of its known first pass effect, POSAs attempt to formulate buprenorphine as intravenous solutions, nasal sprays, sublingual tablets and buccal films. (DTX-077-0001; JTX-248-0001; DTX-165-0002; Tr. 91:10-19, 92:14-18, 94:20-95:16, 99:11-15.)

1. Prior Art Specific to BEMA Delivery of Opioids

11. BEMA devices deliver a drug directly to the oral mucosa and thus avoid first pass metabolism. (DTX-173-0001-0002 at abstract, [0002]; JTX-248-0001-0002; Tr. 106:12-107:3, 109:12-21.)

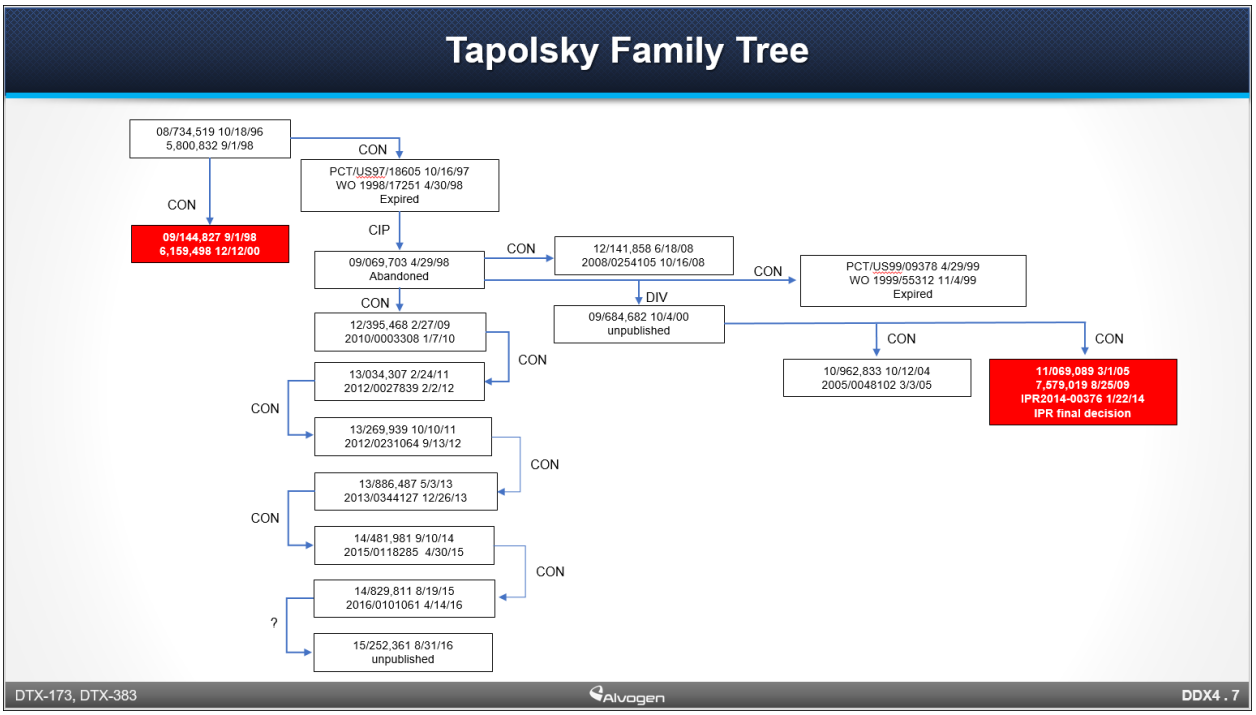
12. Dr. Michniak-Kohn testified about the working mechanism of BEMA devices. (Tr. 131:19-134:9.) Generally, the user applies the BEMA device to the cheek inside the mouth ("buccal surface"). (Tr. 132:3.) Saliva in the mouth (which is mostly water) activates the mucoadhesive polymers, causing the BEMA device to adhere to the mouth. (Tr. 132:3-13.) As the saliva penetrates the BEMA device, the polymers in the mucoadhesive layer begin to swell. (Tr. 132:14-17). The pH buffers dissolve in the saliva and lower its pH, allowing it to dissolve and ionize the buprenorphine. (Tr. 132:14-20; 132:22-133:6, 133:15-21.) The dissolved and ionized buprenorphine then moves through the mucoadhesive layer by concentration gradient and permeates the mucosal surface, where it is absorbed into the bloodstream. (Tr. 133:10-134:2.)

13. Saliva and mucous (or mucus) are used interchangeably herein. Each is predominately water. (Tr. 131:19-132:13, 701:13-15.)

(a) Tapolsky (2005)

14. Tapolsky is a family of patents. (Tr. 112:25-113:8.) Tapolsky 2005 is the patent application publication that resulted in U.S. Patent 7,579,019, and is

related to U.S. Patents 5,800,832 and 6,159,498, which are incorporated by reference into the '866 and '843 patents. (JTX-001 at 13:1-4; Tr. 113:9-18.) The pharmaceutical development report for Belbuca® states that BEMA technology "followed the invention of the mucoadhesive system described in Patent No. 6,159,498," i.e., Tapolsky. (DTX-024-00005; Tr. 113:19-114:16;117:3-21.)



15. Tapolsky discloses the BEMA devices incorporated by reference and claimed by the patents-in-suit for buprenorphine. (JTX-001 at 13:1-4; Tr. 112:24-114:15, 117:3-20.)

16. Because Tapolsky discloses more than 200 active agents, including butorphanol, which is a "prototypical agonist-antagonist opioid analgesic agent," a POSA would have reasonably expected Tapolsky's BEMA devices to deliver

buprenorphine. (DTX-173 at [0046]-[0053]; DTX-362-0001 at abstract; Tr. 110:18-112:1, 112:16-23, 121:9-17, 129:23-130:19, 261:4-262:3.)

17. Tapolsky discloses a BEMA device for any active agent, such as opioids like butorphanol that would benefit from transmucosal delivery. (DTX-173 at [0002], [0013], [0046]-[0053], [0131]; Tr. 106:10-107:3, 111:3-112:4, 112:16-23.)

18. The '866 and '843 patents disclose butorphanol as an exemplary opioid amongst 57 other opioids, including buprenorphine. (JTX-001-0010 at 9:58; JTX-002-0012 at 10:9))

19. During prosecution, in a petition to the Commissioner of Patents to accelerate examination of the '866 patent, BDSI stated, "Tapolsky is Applicant's own patent" and, falsely, "does not teach administration of an opioid." (JTX-004-0033.)

20. Tapolsky's BEMA device is for administration to a mucosal (e.g., buccal) surface. (DTX-173 at [0002], [0024], [0027], Example 20, [0100], [0128]; Tr. 129:23-130:19, 109:22-110:17, 247:13-16, 247:25-248:16.) Tapolsky discloses a method for the direct transmucosal administration of drug, which provides effective drug delivery. (D.I. 114 at 4; DTX-173 at [0024]; JTX-001-0009 at 7:9-11; Tr. 106:12-107:3.)

21. Tapolsky's BEMA device is a layered film disk including a water-erodable adhesive layer including drug and a water-erodable backing layer. (DTX-173 at [0013], [0030]; Tr. 106:17-107:3.)

22. Tapolsky's BEMA device contains an adhesive layer including a film-forming water erodible polymer, such as hydroxyethyl cellulose or hydroxypropyl cellulose, and a bioadhesive polymer, such as sodium carboxymethylcellulose. (DTX-173 at [0031]-[0032]; Tr. 107:4-6, 107:15-109:4; *see* D.I. 249 at 2.)

23. Tapolsky's polymers for the adhesive layer are the same polymers described in the patents-in-suit and utilized in Belbuca®. (JTX-233-023; DTX-173 at [0031]-[0032]; JTX-001-012 at 13:62-63, 14:12; JTX-002-014 at 14:19-20, 14:36-37; Tr. 108:11-18.)

24. Tapolsky's BEMA device also contains a non-adhesive backing layer disposed adjacent to the adhesive layer to provide unidirectional delivery of the drug towards the mucosal surface and to minimize swallowing. (DTX-173 at [0020], [0021], [0030], [0058]-[0062], FIG. 1, FIG. 2; Tr. 109:12-21).

25. Tapolsky discloses a unidirectional diffusion gradient that saliva penetrates in order to move the drug across the polymeric diffusion environment upon application of the device to a mucosal surface. (DTX-173 at [0020], [0021], [0030], [0058]-[0062], FIG. 1, FIG. 2; Tr. 106:20-107:3, 109:12-21, Tr. 109:12-110:17, 129:23-130:19, 247:13-16, 247:25-248:16.)

26. Tapolsky discloses suitable polymers for the backing layer, including a water-erodible, film-forming polymer such as hydroxyethyl cellulose or hydroxypropyl cellulose. (DTX-173 at [0035]; Tr. 109:5-11; *see* D.I. 249 at 2.)

27. Tapolsky's polymers for the backing layer are the same polymers described in the patents-in-suit and utilized in Belbuca®. (JTX-233-0023; JTX-001-0013 at 15:36; JTX-002-0015 at 15:62-63; Tr. 107:15-108:10, 109:7-11.)

28. Tapolsky's BEMA devices "yield fast onset of activity," i.e., rapid and efficient delivery, as well as "excellent bioavailability, and sustained delivery," i.e., enhanced uptake. (DTX-173-0015 at [0131]; *see also* DTX-173-0001 at abstract; Tr. 106:17-107:3.)

29. Tapolsky's BEMA devices provide drug delivery that achieves effective plasma concentration beyond four hours. (DTX-173 at Table 5; Tr. 346:2-14.)

(b) Moro (2003)

30. Like Tapolsky, Moro discloses BEMA technology incorporated by reference by the patents-in-suit. (JTX-001 at 13:1-4; DTX-178 at [0001], [0010], [0035], [0046]; Tr. 117:22-118:11, 121:2-121:8, 121:18-25.)

31. Moro discloses an extensive list of active agents. (DTX-178 at [0047]-[0065]; Tr. 120:8-16). Moro discloses a BEMA device for any active agent

that would benefit from transmucosal administration. (DTX-178 at [0035], [0047]-[0065]; Tr. 118:8-11.)

32. Moro discloses BEMA delivery of "analgesic narcotics," including buprenorphine specifically. (DTX-178-0005-0008 at [0035], [0046], [0064]; Tr. 117:22-118:11, 118:12-22, 120:13-16.)

33. The Moro device contains an adhesive layer including a film-forming polymer, such as hydroxyethyl cellulose or hydroxypropyl cellulose, and a bioadhesive polymer, such as sodium carboxymethylcellulose. (DTX-178-0006 at [0041]; Tr. 118:23-119:10; *see* D.I. 249 at 4.)

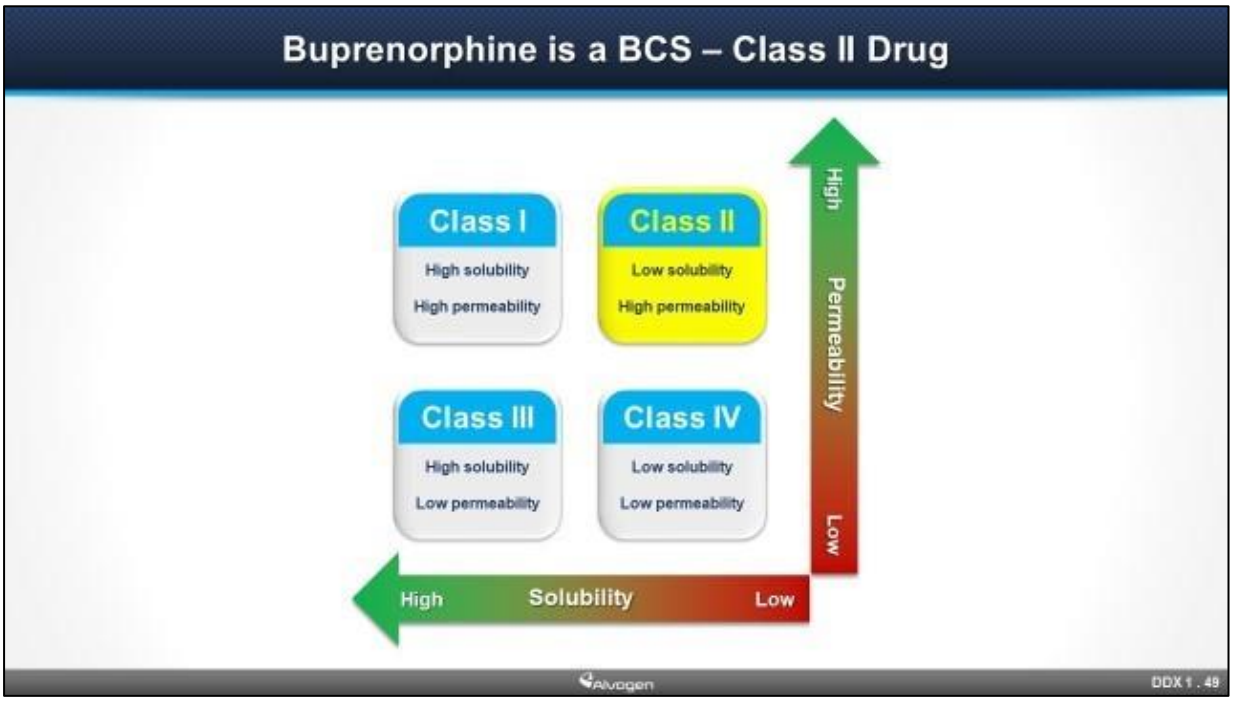
34. The Moro device also contains a non-adhesive backing layer including a film-forming polymer such as hydroxyethyl cellulose or hydroxypropyl cellulose (*see* D.I. 249 at 4), which maximizes unidirectional delivery of drug toward the mucosal surface while minimizing swallowing of the drug. (DTX-178-0006 at [0043]; Tr. 119:11-120:7.)

35. Moro's polymers for the mucoadhesive and backing layers are the same polymers described by the patents-in-suit and utilized in Belbuca®. (JTX-233-0023; DTX-178-0006 at [0041], [0043]; JTX-001-0012-0013 at 13:62-63, 14:12, 15:36; JTX-002-0014-0015 at 14:19-20, 14:36-37, 15:62-63; Tr. 108:11-18, 118:23-119:17.)

2. Prior Art Specific to Buprenorphine Properties

36. Buprenorphine hydrochloride[2] is the salt form of buprenorphine that formulators use in pharmaceutical formulations. (*See* JTX-003-0012 at 9:61-62; JTX-248-0002.)

37. Buprenorphine is a BCS-II ("Biopharmaceutics Classification System - Class II") drug, which means that the drug has low solubility in saliva but high permeability (lipophilicity). (Tr. 699:18-701:5.)



38. If the formulation buffers the saliva to a pH capable of ionizing and dissolving the buprenorphine, then the buprenorphine will readily permeate the

[2] The terms "buprenorphine" and "buprenorphine hydrochloride" are used interchangeably herein.

mucosal membranes and absorb into the bloodstream. (Tr. 131:19-134:9, 699:18-701:5.)

(a) Johnson (2005)

39. Johnson summarizes what POSAs knew about buprenorphine prior to the patents-in-suit. Specifically, that buprenorphine: (1) is a highly potent and effective analgesic for the treatment of pain with a long duration of action; (2) has a wider safety profile compared to other opioids, especially with regard to respiratory depression; (3) has low abuse potential and fewer symptoms of withdrawal; (4) experiences high first pass effect (and should be administered transmucosally, for example, to avoid liver metabolism); and (5) is extremely lipophilic (meaning that it will permeate mucosal membranes when dissolved and ionized). (DTX-165-0001-0003, 0005, 0007-0009, 0020-0021; Tr. 96:4-98:22, 484:25-486:25.)

40. At trial, BDSI agreed that Johnson teaches that buprenorphine has limited abuse potential because of a ceiling effect at higher doses, and has a wider safety potential compared to full mu agonists. (DDX4-5; Tr. 143:23-24.)

(b) Bullingham I (1981)

41. Bullingham I discloses the same properties of buprenorphine described in Johnson. (DTX-077-0001, 0005; Tr. 91:2-19, 93:25-94:9.) Bullingham I teaches that buprenorphine was well suited for oral transmucosal

administration because of its high lipophilicity, high potency, high first pass effect, long duration of action, and low abuse potential. (DTX-077-0001; Tr. 91:2-19, 92:19-25, 99:7-10; *see* D.I. 249 at 3.) Bullingham I teaches that sublingual delivery of buprenorphine is effective because of these "specific features of buprenorphine." (DTX-077-0005; Tr. 93:25-94:9; *see also* JTX-248-002.)

42. Bullingham I reports that the sublingual (i.e., transmucosal) administration of buprenorphine provides a first quantifiable concentration (i.e., T_{first}) of buprenorphine between 40 and 60 minutes once the background intravenous dose is excluded. (DTX-077-0003 (Table 2); Tr. at 334:10-335:17.)

43. At trial, BDSI agreed that Bullingham I teaches that buprenorphine is highly potent, has a long duration of action with low abuse potential, and is highly lipophilic. (DDX4-5; Tr. 142:24-143:11; *see also* D.I. 249 at 3.)

44. Bullingham I discloses that the onset of pain relief from the sublingual dose of buprenorphine "occurred between 15 and 45 minutes." (DTX-077-0003; Tr. 338:25-339:20).

45. Bullingham I also discloses that the sublingual administration of buprenorphine maintains an average duration of analgesia for 534 minutes. (DTX-077-0003.) Bullingham I teaches maintaining effective buprenorphine concentrations for more than four hours. (DTX-077-0003; Tr. 344:16-345:7.)

3. Prior Art Specific to pH

46. Saliva is not ideal for dissolving buprenorphine due to its near-neutral pH. (JTX-249-0004; Tr. 133:15-21, 147:7-23.)

47. pH is the measure of how acidic or basic a liquid is relative to neutral water. (Tr. 146:13-147:6.) pH is logarithmic, such that each unit is an order of magnitude greater or lesser than its adjacent units. (Tr. 146:22-147:6.) For example, a pH of 4 is 10X more acidic than a pH of 5 and 100X more acidic than a pH of 6. (*See* Tr. 146:13-147:6.)

48. POSAs understood buprenorphine to be poorly soluble in water. (JTX-248-0004, 0007-0008, Tr. 131:19-133:21, 153:9-24.)

49. POSAs also understood that buprenorphine solubility is highly pH-dependent, having the highest solubility at low (i.e., strongly acidic) pH values. (JTX-248-0004; Tr. 147:7-23; 166:12-23.)

50. "Solubility" is the maximum concentration of drug than can dissolve in a solvent (e.g., water). (Tr. 139:1-2.)

51. "Dissolution" is the rate the drug dissolves in the solvent. (Tr. 139:3-4.)

52. At acidic pH values below 6, buprenorphine is ~100% ionized. (JTX-248-0004; Tr. 133:2-133:6, 133:15-21; 166:12-23, 175:3-6, 671:16-672:7.)

53. "Ionization" is the process by which the neutral drug salt converts to electrically charged "ions" in solution. (Tr. 139:5-6.) Like solubility, ionization of buprenorphine is highly pH-dependent. (Tr. 146:8-12.)

54. The entire prior art of record demonstrates that formulators provided buprenorphine in acidic pH environments where it is ~100% ionized. (JTX-249-0006; DTX-377-002-0004; Tr. 168:24-170:22, 162:14-164:9, 170:5-9; DTX-172-0004; Tr. 167:18-168:23; DTX-203 at [0010], [0071], [0083]; Tr. 171:3-172:22; DTX-174-0003-0004 at 2:11-3:4; Examples 1-18; Tr. 174:12-175:6, 671:16-673:25.)

55. None of the prior art relied on by Dr. Williams teaches that buprenorphine is subject to a "general rule" that unionized drugs permeate the mucosa better. (Tr. 664:11-670:20.)

56. The trial record does not include any reference where a formulator attempted to provide buprenorphine in a neutral or basic environment, or where the buprenorphine was less than ~100% ionized. (Tr. 176:1-176:9, 201:14-202:17.)

(a) Cassidy (1993)

57. Cassidy teaches that the solubility of buprenorphine is highly pH dependent, with the highest solubility seen at low (acidic) pH. (JTX-248-0004; Tr. 147:7-23.)

58. Cassidy teaches that buprenorphine solubility at "neutral pH," i.e., pH 7.3, is "considerably lower." (JTX-248-0004; Tr. 147:7-23.)

59. Figure 1 of Cassidy illustrates buprenorphine solubility, i.e., the amount of buprenorphine (mg/mL) that can be dissolved in each of three different buffers, i.e., phosphate, USP phosphate, and physiological (TPS), versus pH (from 4 to 8) on a logarithmic scale. (JTX-248-0004 at Figure 1; Tr. 138:14-139:2, 147:24-148:14.)

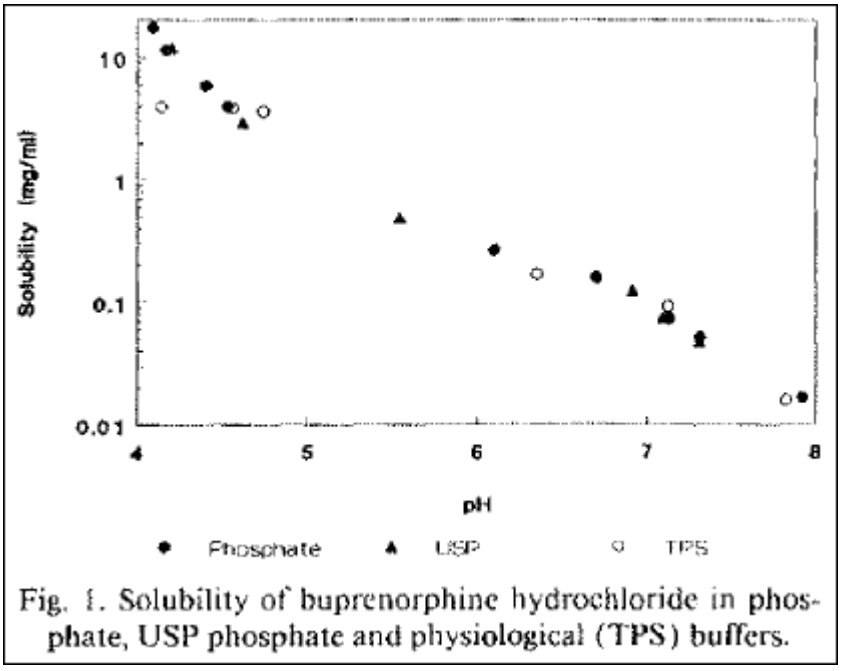
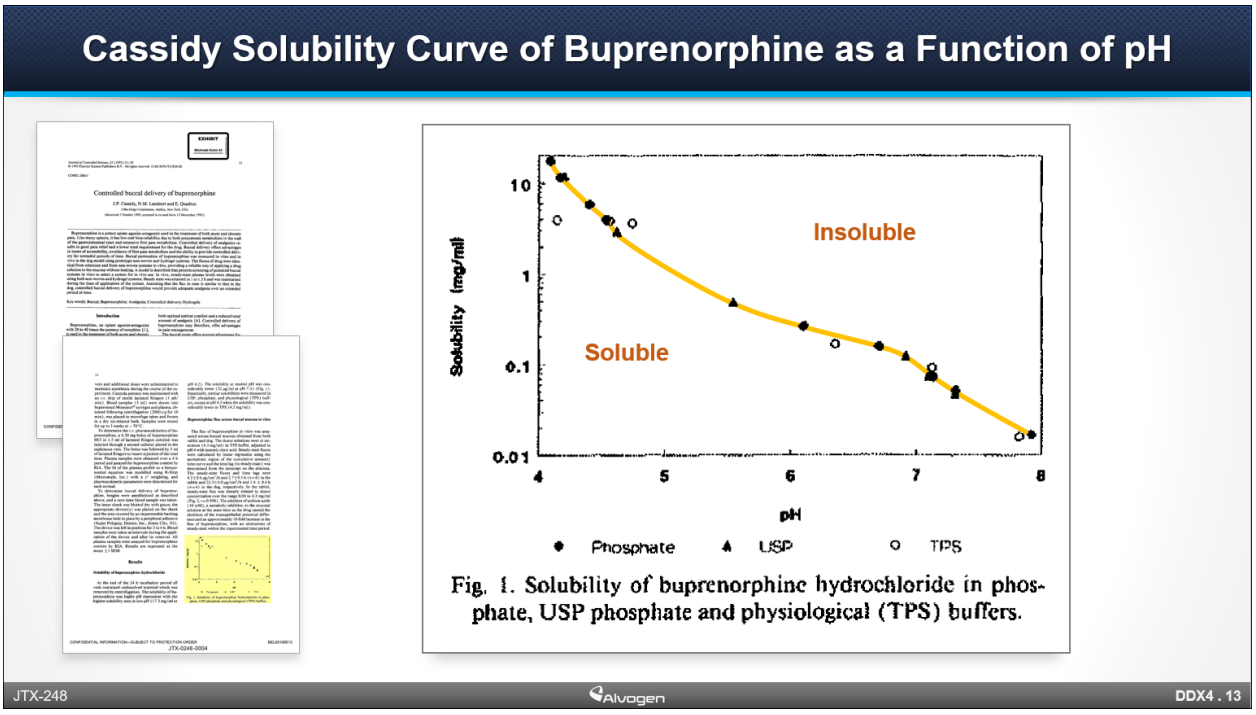


Fig. 1. Solubility of buprenorphine hydrochloride in phosphate, USP phosphate and physiological (TPS) buffers.

60. Cassidy reports that similar buprenorphine solubilities were measured in each buffer system, except at pH 4.2, where buprenorphine solubility in TPS buffer was "considerably lower" than in the other two buffers because of the reduced buffering capacity of TPS at this low pH. (JTX-248-0004; Tr. 148:15-

150:9). The point at pH 4.2 in TPS buffer is an outlier. (JTX-248-0004; Tr. 148:15-150:9.)

61. Setting aside the point at pH 4.2 for TPS buffer, which Cassidy characterizes as an outlier, Dr. Michniak-Kohn annotated Figure 1 as follows:

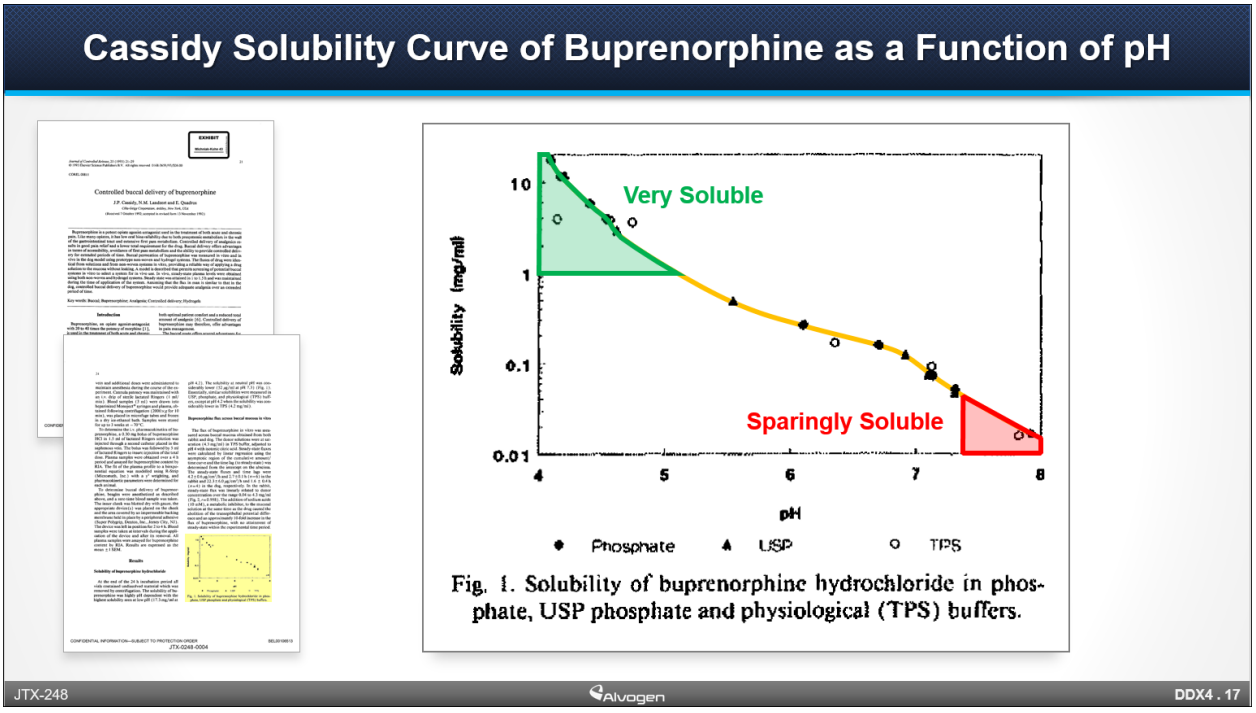


(DDX 4-13; JTX-248-0004 at Figure 1; Tr. 148:15-150:9, 150:19-151:5.)

62. Points that fall below the line represent soluble buprenorphine, while points that fall above the line represent insoluble buprenorphine. (JTX-248-0004 at Figure 1; Tr. 150:19-151:5.)

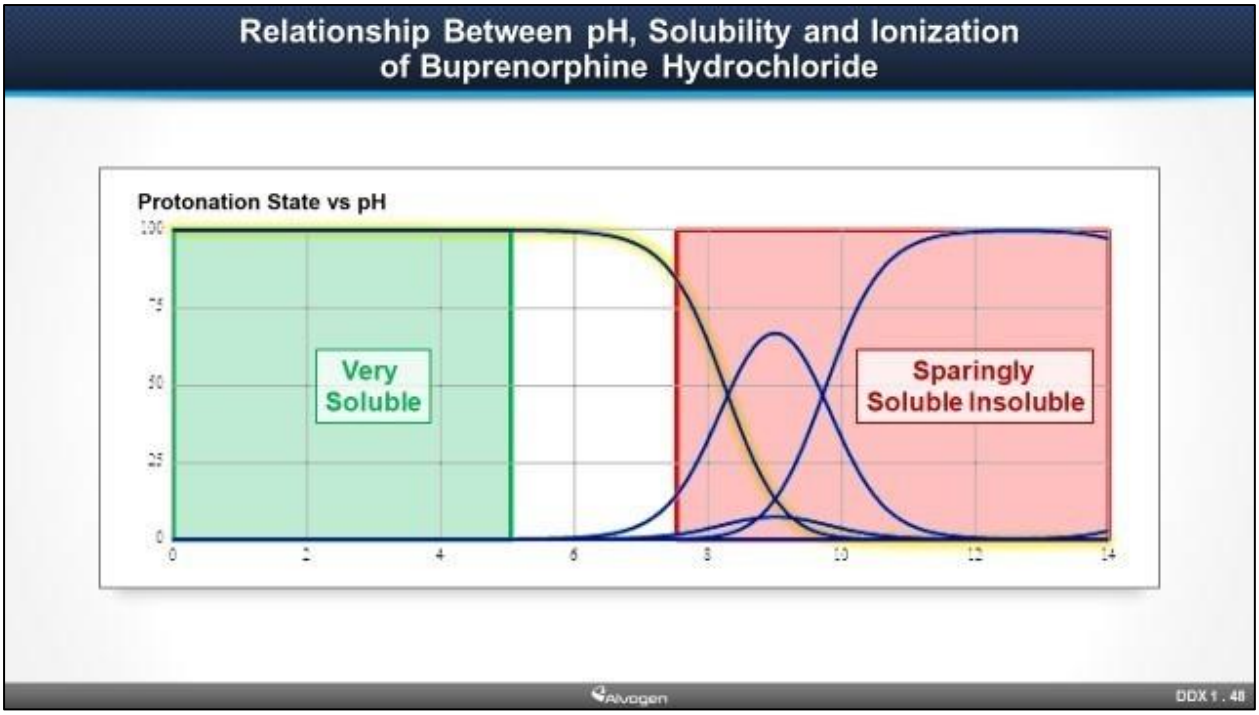
63. Figure 1 of Cassidy illustrates that the highest solubility of buprenorphine is obtained below a pH of about 5. (JTX-248-0004 at Figure 1; Tr. 150:12-18.)

64. Figure 1 of Cassidy (as annotated by Dr. Michniak-Kohn) illustrates that buprenorphine is "very soluble" at pH values below 5, and is "sparingly soluble" to insoluble at pH values above 7.5.



(DDX 4-17; Tr. 151:25-153:2.)

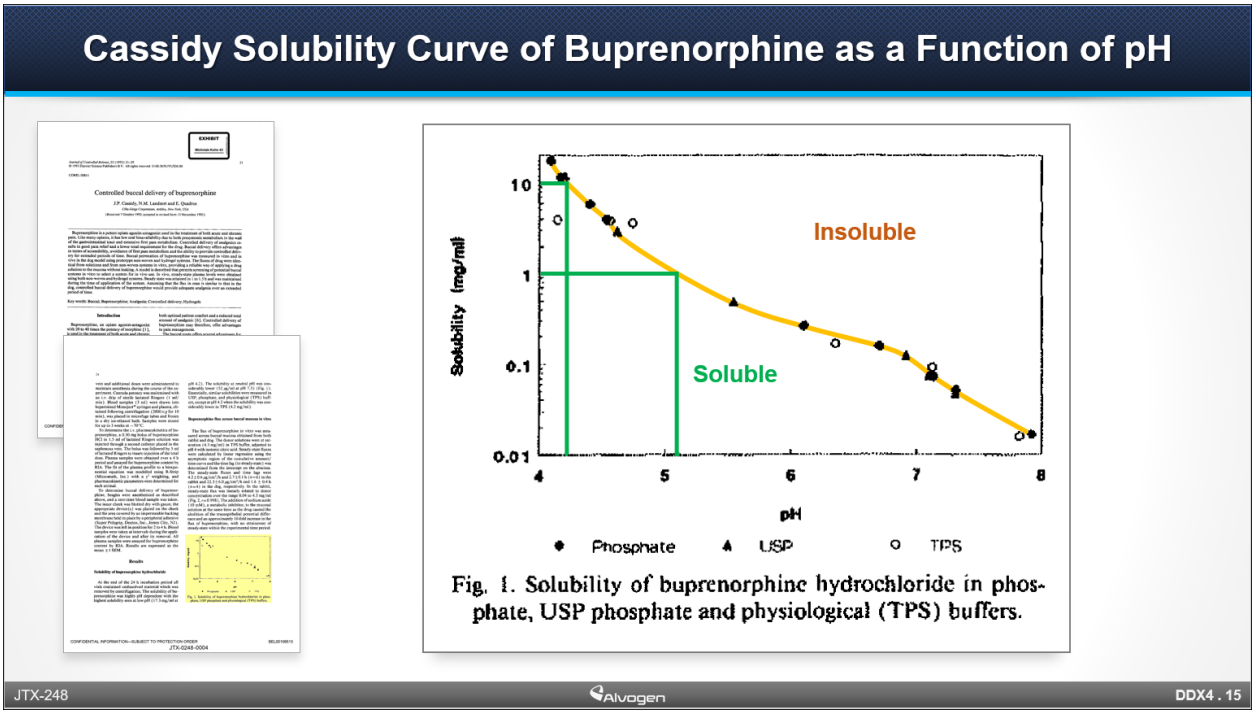
65. Based on the calculations performed by Dr. Stephen Davies (BDSI's chemistry expert), a POSA would have understood that buprenorphine is 100% ionized at pH values below 5 where it is "very soluble." (DTX-377-0002, 004; Tr. 162:14-164:19; 165:21-166:11.)



(DDX 4-20.)

66. A POSA would have been able to generate Dr. Davies' ionization data by using the well-known Henderson-Hasselbalch equation that relates pH, pKa, and the log ratio of ionized and unionized portions of a molecule. (Tr. 162:14-164:4.)

67. Cassidy further illustrates to a POSA that buprenorphine solubility increases exponentially as pH decreases from 5 to 4, which anticipates the pH ranges claimed in the patents. (JTX-248-0004, Figure 1; JTX-248-007-0008; Tr. 152:14-153:2, 153:9-20.)



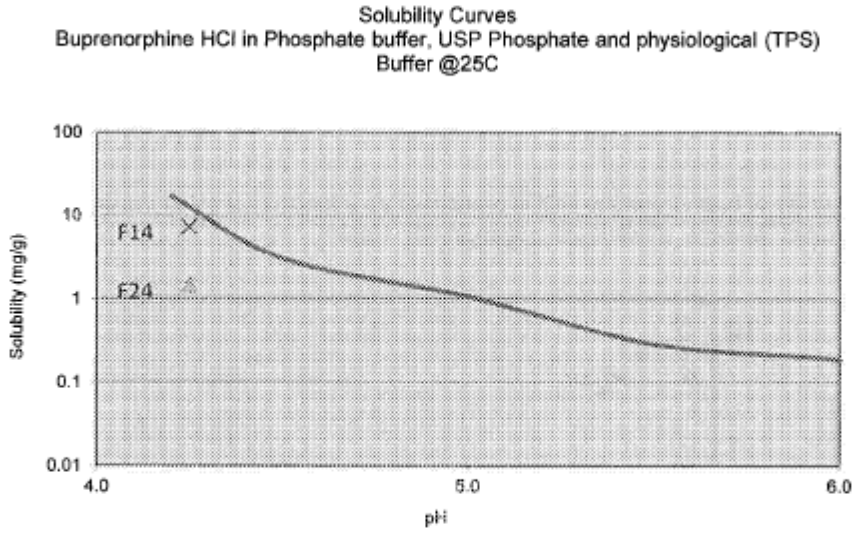
(DDX 4-15.)

68. As shown by the illustration, at a pH of about 5, about 1 mg/mL buprenorphine is soluble, but at a pH of about one unit less, i.e., at a pH of just above 4, about 10 mg/mL buprenorphine is soluble. (JTX-248-0004, Figure 1, JTX-248-0007-0008; Tr. 151:17-24.) Because the pH scale is logarithmic, a 10-fold increase in solubility per one unit drop of pH represents an exponential increase in solubility. (JTX-248-004, Figure 1, JTX-248-0007-0008; Tr. 151:17-24.)

69. At acidic pH values, a one unit change in pH changes buprenorphine solubility by a factor of 10. (JTX-248-0004, Tr. 151:17-24.)

70. A BDSI development report for Belbuca® cites Cassidy directly, and states "[a]s per the literature, the solubility of buprenorphine at approximately pH 7.8 is 100x less that the solubility of buprenorphine at a pH of approximately 5." (DTX-370-0018.) The development report reproduced Cassidy Figure 1, but does not include data relating to the outlier point at pH 4.2 for TPS buffer. (JTX-248-0004; Tr. 148:15-150:9, 680:17-681:23.) The development report states that the final Belbuca® product formulations (F14 and F24) were "formulated in the pH of highest [aqueous] solubility" as well as at concentrations lower than the solubility limit of the polymer system. (DTX-0370-0018-0019; JTX-248-0004; *see* Tr. 681:6-9.)

Figure 6 The concentration of F24 and F14 Formulations as a function of pH and comparison to the Journal of Controlled Release, Volume 25, pages 21-29, 1993.



In addition to the literature comparison, the solubility of buprenorphine in the mucoadhesive blend was explored at different pH conditions. F14 and F24 mucoadhesive blend formulations were formulated in the pH of highest solubility and at concentrations lower than the solubility limit as shown in Figure 7. As a result, the particle size for the API is not a critical attribute.

(DTX-370-0019.) Dr. Williams confirmed that this reference to the highest aqueous solubility refers to Cassidy data. (Tr. 681:24-682:8.)

71. BDSI recognized the importance of the aqueous solubility of buprenorphine, as described by Cassidy, in formulating Belbuca®. (DTX-370-0019; JTX-248-004; Tr. 680:12-682:8.)

72. During manufacture, buprenorphine and the polymers dissolve in water, which is later removed during the drying process. (Tr. 674:19-675:7.) A POSA would know that in the final product, buprenorphine exists as a solid and must dissolve and ionize in the saliva in order to leave the dosage form and

permeate the membrane. (Tr. 132:14-134:2, 701:6-702:3.) The solubility of buprenorphine in the polymer casting solution is not relevant to the requirement that buprenorphine be soluble in saliva. (Tr. 201:14-19, 202:18-25, 701:6-702:5.)

(b) Weinberg (1988)

73. Weinberg teaches that buprenorphine has the highest partition coefficient (and is the most lipophilic) as compared to eight other known opioids. (JTX-249-0002, Table 1; Tr. 137:20-138:13.)

Table I. The concentration, partition coefficient, and pKa of study opioids

Drug	*Concentration (mg/ml)*	*PC**	*pKa†*
Morphine	5.0	0.00001	7.9
Hydromorphone	1.0	0.0001	NA
Levorphanol	1.0	0.01	9.4
Heroin	2.5	0.04	NA
Fentanyl	0.05	19.6	8.4
Methadone	5.0, 0.8	44.6	9.3
Buprenorphine	0.1	60.3	NA
Oxycodone	2.5	NA	NA
Naloxone	1.0	NA	7.9

PC, partition coefficient; NA, not available.
Partition coefficients and pKa values compiled from references 15 through 18.
*Heptane and phosphate buffer at pH 7.4.
†At 37° C.

74. Because of its partition coefficient, which reflects its tendency to go into lipid environments of cell membranes, a POSA would have expected buprenorphine, in its fully ionized form, to permeate the lipid environment of the mucosal membrane. (Tr. 135:11-136:12, 136:18-24.)

75. Weinberg reports that buprenorphine, at pH 6.5, where a POSA would have known buprenorphine to be nearly 100% ionized, absorbs well across the oral mucosa. (JTX-249-0006; Tr. 168:24-171:2.)

76. Weinberg teaches that the poor solubility of buprenorphine at pH 6.5 prohibits the formulation of buprenorphine at higher, basic pH values. (JTX-249-0006; Tr. 170:10-22.)

(c) Todd (1983)

77. Todd states, "[b]uprenorphine is a potent antagonist analgesic with good bioavailability following sublingual administration, useful in the relief of moderate to severe pain and also in the treatment of narcotic addiction." (DTX-174-0001 at abstract; Tr. 173:18-174:6.)

78. Todd recognizes that "[b]uprenorphine effectively relieves moderate to severe pain in doses of 0.15 mg or more administered either parenterally or sublingually," and discloses that the "optimum therapeutic range" for buprenorphine sublingual tablets is 0.2 to 0.4 mg. (DTX-174-0002 at 1:9-14.)

79. Todd teaches aqueous solutions of buprenorphine for sublingual administration. (DTX-174-0001 at abstract.)

80. Todd states, "We have now developed stable liquid compositions containing buprenorphine at a high concentration suitable for sublingual administration. According to the present invention there is provided a pharmaceutical composition for sublingual administration comprising buprenorphine or a non-toxic salt thereof dissolved in 20-30% v/v aqueous ethanol buffered to between pH 4.5 to 5.5 with 0.05 to 0.2 molar concentration of a

buffering agent." (D.I. 249 at 2; *see also* DTX-174-0003-0004 at 2:21-3:4, Example 17.)

81. Todd teaches a finite number of acidic pH values for its sublingual buprenorphine solutions, i.e., pH 4, 5, and 6, each of which provide "uptake," i.e., absorption, of buprenorphine that a POSA would have known was ~100% ionized. (DTX-174-0003 at 2:11-17; Tr. 174:12-175:25.)

82. Todd also includes 18 examples of buprenorphine formulations buffered to a pH between 4.5 and 5.5, including at a pH of 4.5, at a pH of 5, and at a pH of 5.5, where a POSA would have known buprenorphine to be 100% ionized. (DTX-174-0005-0007 at 4:5-6:19; Tr. 175:16-25, 671:16-672:7.)

83. Citric acid/sodium citrate buffers, the same buffers used in Belbuca®, are disclosed by Todd and used in one of its examples. (DTX-174-0003-0004 at 2:21-3:4, DTX-174-0005 at Example 1, DTX-174-0007 at Example 17; Tr. 173:18-174:2.)

84. Dr. Williams criticized Todd because the aqueous solutions utilize water and ethanol as co-solvents. (DTX-174-0003-0004 at 2:21-3:4; Tr. 173:18-174:2, 652:21-653:21.)

85. However, Tapolsky teaches that its device preferably includes a combination of water and ethanol as solvents. (DTX-173-0009 at [0063].)

86. The ’866 and ’843 patents also describe water as the solvent, and do not preclude the use of ethanol as a co-solvent. (JTX-001-0015 at Example 1, 19:21-22, 40-42, 018 at Example 3, 25:45-53.) Furthermore, the patents prefer ethanol as a disintegration aid that can be included in the claimed buprenorphine devices to “increase the disintegration rate and shorten the residence time of the device ….” (JTX-001-0012 at 17:7-15; Tr. 672:8-674:1.)

(d) Commercial Suboxone® Sublingual Tablets (2002)

87. In 2002, FDA approved Suboxone® sublingual tablets. (JTX-471-0003; Tr. 480:12-482:2.)

88. As noted in the label, Suboxone® includes buprenorphine hydrochloride and pH buffers (citric acid/sodium citrate). (DTX-172-0002; Tr. 153:25-154:10, 160:17-25, 694:3-23.)

89. Citric acid/sodium citrate are the same buffers used in Belbuca®. (JTX-233-0023, Tr. 174:7-11, 694:21-23.)

90. A POSA would have understood the pH buffers in Suboxone® would reduce the pH of saliva to allow it to dissolve and ionize the buprenorphine. (Tr. 131:19-134:9, 160:17-25.)

91. BDSI submitted the Declaration of Dr. Maureen Reitman to the PTO in the context of an *Inter Partes* Review, where BDSI sought to establish the pH of Suboxone® in order to invalidate a competitor's patent. (DTX-365-0001, 0003.)

92. Following a simple, well-accepted procedure, Dr. Reitman determined that Suboxone® provides a pH of 3.5 in solution. (DTX-365-0003 at ¶¶ 4-5; Tr. 161:6-162:3; *see also* Tr. 695:19-696:2.)

93. To determine the pH, Dr. Reitman placed the tablet and a pH meter into deionized water and measured the pH of what was produced. (Tr. 161:15-23.)

94. BDSI admitted to the PTO that the pH of Suboxone® was inherent to the tablets and known to be 3.5. *See* Petition, *BioDelivery Sciences Int'l, Inc. v. RB Pharms. Ltd.*, IPR2014-00325, Paper 8 (PTAB filed Jan. 15, 2014) at pp. 6, 10.[3] According to BDSI, the pH "can be readily obtained in a matter of minutes by anyone with deionized water and a pH meter." (*Id*. at p. 42; *see also* Tr. 695:19-696:3.)

95. The trial record demonstrates that a POSA would have understood that Suboxone®, at a pH of 3.5, provides transmucosal absorption of 100% ionized buprenorphine. (DTX-365-0003 at ¶ 5; DTX-172-0004; Tr. 154:11-16, 160:17-162:3, 167:18-168:23.)

[3] This document is the publicly-available petition that BDSI submitted to the Patent Office, which attached the Reitman Declaration in support of a request for inter partes review of U.S. Patent No. 8,475,832. This document itself is not in evidence, but should be considered with the Reitman Declaration.

(e) Birch (2005)

96. Birch discloses aqueous buprenorphine solutions, which can "induce rapid and prolonged analgesia when delivered intranasally to a patient." (DTX-203-0001 at abstract.)

97. The solutions have a pH between 3 and 4.8, where a POSA would have understood buprenorphine to be 100% ionized, and provide "rapid uptake" of buprenorphine across the nasal mucosa into the plasma. (DTX-203 at [0010]-[0021], [0071], [0083]; Tr. 171:3-172:22.)

B. Claims 3 and 10 of the '866 Patent and Claims 8, 9, and 20 of the '843 Patent Are Obvious

98. The BEMA delivery device of Tapolsky satisfies all requirements of claims 3 and 10 of the '866 patent, and claims 8, 9, and 20 of the '843 patent, except that Tapolsky does not disclose buprenorphine, and does not disclose that the polymeric diffusion environment is buffered to the claimed pH ranges. (Tr. 109:22-110:17.)

99. BDSI did not offer any contrary testimony regarding the disclosure of Tapolsky. (Tr. 650:22-652:7.)

1. It Was Obvious to Utilize Buprenorphine in Tapolsky

100. A POSA would have been motivated to use buprenorphine in Tapolsky's BEMA platform because of the known properties of buprenorphine, and because the prior art taught its formulation in a BEMA device for buccal

delivery. (Tr. 112:16-23, 129:23-130:19; *see also* Tr. 109:12-110:17, 247:13-16, 247:25-248:16.)

101. Johnson teaches that buprenorphine has been available as a parenteral and sublingual analgesic since the 1970s, and "has been found to be amenable to new formulation technology based on its physiochemical and pharmacological profile." (DTX-165-0001; Tr. 96:15-25; *see* D.I. 249 at 5.)

102. Cassidy taught that buprenorphine is 20-40 times more potent than morphine. (JTX-248-0001; Tr. 94:20-25, 99:11-15; *see* D.I. 249 at 4.) Cassidy recognized that buprenorphine has high first pass effect but suggested that buccal delivery "offers advantages in terms of accessibility" while providing "the ability to provide controlled delivery for extended periods of time." (JTX-248-0001; Tr. 94:20-96:2.) A POSA would have known that "administration of an analgesic at a constant rate results in both optimal patient comfort and a reduced total amount of analgesic," such that "[c]ontrolled delivery of buprenorphine may, therefore, offer advantages in pain management." (JTX-248-0001; Tr. 94:20-96:2.)

103. At trial, BDSI agreed that Cassidy teaches that buprenorphine is 20-40 times more potent than morphine and has a high first pass effect. (DDX4-5; Tr. 143:12-13; *see also* D.I. 249 at 4.)

104. A POSA would have known from Johnson, Bullingham I, and Cassidy that buprenorphine is a potent opioid analgesic that is highly lipophilic, meaning it

absorbs well even in ionized form, and experiences high first pass effect requiring transmucosal or other delivery that avoids liver metabolism. (DTX-165-0001-0003, 0005, 0008-0009; Tr. 96:4-98:22, 485:1-487:1; DTX-077-0001, 0005; Tr. 91:2-19, 93:25-94:9; JTX-248-0001-0002; Tr. 94:16-96:2.)

105. A POSA also would have known from Johnson, Bullingham I, and Cassidy that the oral transmucosal administration of buprenorphine provides an effective, convenient delivery route that avoids the first pass effect. (DTX-077-0001,0005; JTX-248-0001; DTX-165-0002; Tr. 91:10-19, 92:14-18, 93:8-13, 94:20-95:16, 99:11-15.)

106. Cassidy teaches that buccal devices could improve bioavailability by providing unidirectional delivery that avoids loss due to swallowing. (JTX-248-0001; Tr. 95:10-13.)

107. Yang, Chen and Das illustrate the broad application of the BEMA platform to opioids like buprenorphine.[4] (DTX-175 at [0014], [0131]; DTX-176-0005-0006, 0008; DTX-323-0003; Tr. 123:14-124:3, 124:4-125:68 128:16-129:22.)

108. Yang discloses mucoadhesive polymeric "rapid dissolve film products" for the transmucosal administration of opioids, which can include

[4] Yang, Chen, and Das published prior to July 21, 2006, the earliest possible filing date of the '866 and '843 patents. (DTX-175-0001; DTX-176-0001; DTX-323-0001.)

buffers. (DTX-175 at [0014], [0131], [0133], [0161], [0209]-[0210]; Tr. 128:16-129:22.)

109. Chen teaches a mucoadhesive film including an effective amount of a drug, such as an opiate like hydromorphone, dispersed in a polymeric diffusion environment. (DTX-176-0005-0006, 0008; Tr. 124:4-125:88.)

110. Das predicted that the use of a "mucoadhesive delivery system" for buprenorphine would improve its bioavailability, and describes mucoadhesive tablets and films for sublingual delivery. (DTX-323-0003; Tr. 123:14-124:3.)

111. POSAs believed that a "mucoadhesive delivery system" generally, and BEMA films specifically, could improve bioavailability over sublingual tablets by providing unidirectional delivery that avoids loss due to swallowing. (JTX-248-0001; DTX-323-0003; Tr. 95:10-13.)

112. Tapolsky and Moro teach that BEMA devices can transmucosally deliver opioids generally, and Moro teaches buprenorphine specifically. (DTX-173 at [0046]-[0053]; DTX-362-001 at abstract; DTX-178 at [0035], [0046], [0048], [0064]; Tr. 110:18-112:1, 112:16-23, 121:9-17, 117:22-118:11, 118:12-22, 120:13-16, 129:23-130:19, 261:4-262:3.)

113. Known therapeutic ranges for buprenorphine were 300-600 µg for injection and 200-400 µg for sublingual tablets. (DTX-174-0002 at 1:12-14; DTX-165-0020; Tr. 134:3-5.)

114. Providing an effective amount of an opioid like buprenorphine in the BEMA devices of Tapolsky or Moro would have been a matter of routine skill. (DTX-173 at [0034], [0054]; Tr. 129:23-130:19, 131:19-23, 134:3-5.)

2. It Was Obvious to Buffer Tapolsky to the Claimed pH

115. Claims 3 and 9 of the '866 patent are directed to Tapolsky's BEMA device containing buprenorphine buffered to a pH "between about 4.5 and about 5." (JTX-001-0012, 019 at 13:1-4, claim 3, claim 9.) Claims 8, 9 and 20 of the '843 patent are directed to Tapolsky's BEMA device containing buprenorphine buffered to a pH "between about 4 and about 6." (JTX-002-0014, 0021 at 13:26-32, claim 8, claim 9, claim 20.)

116. "Basic science" and common sense dictate that buprenorphine must dissolve from the BEMA device into the saliva before it can permeate the mucosa. (Tr. 132:14-134:2, 701:13-702:5.) Dr. Williams acknowledged this fact. (Tr. 701:13-702:5.)

117. Dr. Williams testified that buprenorphine is a BCS-II drug, and that a POSA would have known that buprenorphine would absorb across the mucosa if dissolved and ionized—such as in saliva buffered to a pH between 4 and 5. (Tr. 699:18-700:4.)

118. There is no dispute that the solubilization of buprenorphine from a BEMA device is highly pH dependent. (Tr. 133:2-6, 133:15-21, 146:6-12, 689:21-690:7.)

119. In addition, there is no dispute that buprenorphine must ionize in order to dissolve, and its ionization is likewise highly pH dependent. (Tr. 146:6-12; 670:6-20; 671:16-674:1.)

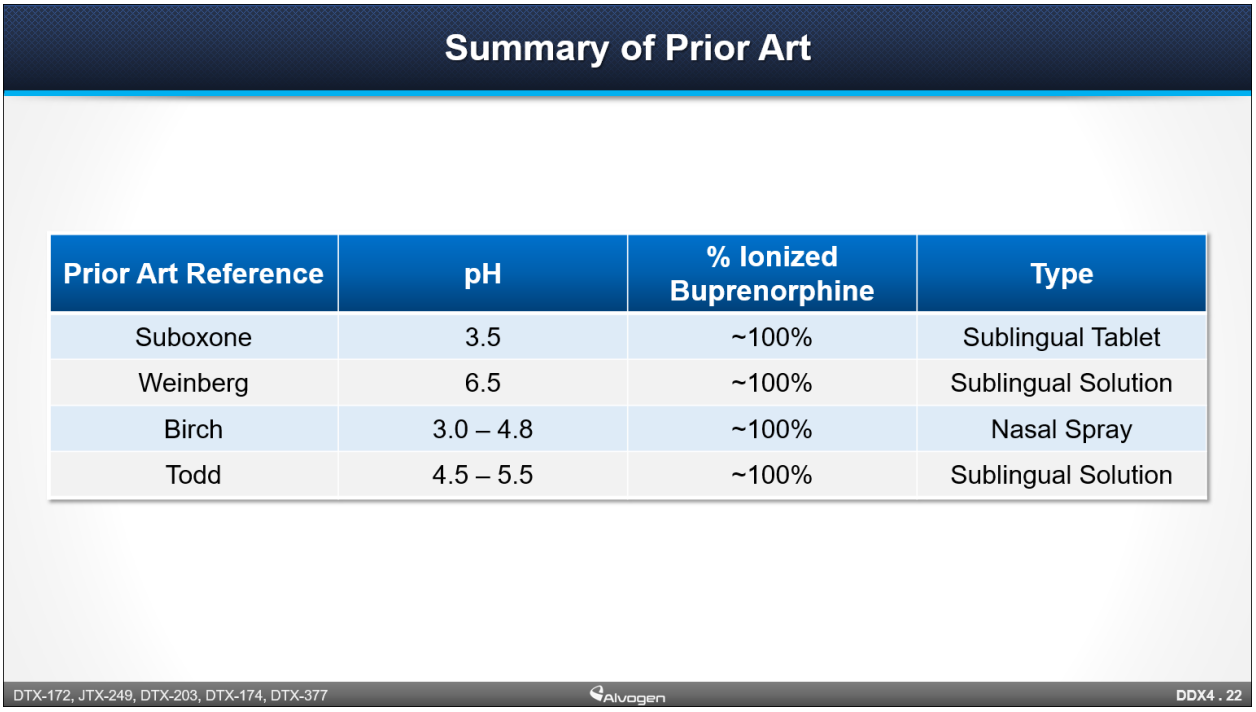
120. The dissolved and ionized buprenorphine then moves through the mucoadhesive layer by concentration gradient and permeates the mucosal surface, where it is absorbed into the bloodstream. (Tr. 132:22-133:14.) A POSA would have known that buprenorphine has to be dissolved to be able to permeate the mucosa. (Tr. 132:22-133:6.)

121. Cassidy shows that the solubility of buprenorphine is highly pH-dependent and increases exponentially as pH drops from 5 to 4, where it remains 100% ionized. (JTX-248-0004, Figure 1; Tr. 147:7-23, 151:17-24; DTX-377-0002, 0004; Tr. 162:14-164:19; 165:21-166:11.)

122. Cassidy shows that the solubility of buprenorphine is highly pH-dependent and increases exponentially as pH drops from 5 to 4, where it remains 100% ionized. (JTX-248-0004, Figure 1; Tr. 147:7-23, 151:17-24; DTX-377-0002, 0004; Tr. 162:14-164:19; 165:21-166:11.)

123. A POSA would have expected that a polymeric diffusion environment of Tapolsky buffered to a pH around these values would provide the highest amount of dissolved and ionized buprenorphine to be available for absorption. (Tr. 146:6-12, 153:9-20, 166:12-23.) Thus, a POSA would have buffered the polymeric diffusion environment of Tapolsky's device to acidic pH values with a reasonable expectation of optimizing the transmucosal absorption of buprenorphine. (Tr. 200:22-201:13.)

124. The prior art corroborates this expectation – pH values of 3-4.8 (Birch), 3.5 (Suboxone®), 4-5 (Cassidy), 4- 6 (Todd), and 6.5 (Weinberg). Regardless of dosage form, prior art transmucosal formulations provide buprenorphine at acidic pH where it is dissolved and ~100% ionized, and demonstrate its absorption. (JTX-249-0006; DTX-174-0003 at 2:11-17; DTX-377-0002, 0004; DTX-365-0003 at ¶ 5; DTX-365-0003 at ¶ 5; DTX-203 at [0010]-[0021], [0071], [0083]; Tr. 154:11-16, 160:17-162:3, 162:14-164:19; 165:21-166:11; 167:18-172:22, 174:12-175:25.)



(DDX 4-22.) Therefore, the prior art confirms that a POSA would have expected dissolved and ionized buprenorphine to readily permeate mucosal membranes at these acidic pH values.

125. Dr. Williams agreed that Todd, for example, taught a POSA that buprenorphine absorbs transmucosally at acidic pH values where it is ~100% ionized. (Tr. 671:16-674:1.)

126. Because the pH of saliva varies from 5.8 to around 7, which is not ideal for dissolving buprenorphine, a POSA would provide buffers in the polymeric diffusion environment that dissolve in and acidify the saliva. (Tr. 153:9-24.)

127. The prior art taught that buffer systems maintain active agents in their ionized form to help "overcome the influence of the conditions of the surrounding environment, such as rate of saliva secretion, pH of the saliva, and other factors." (JTX-462 at [0057], Table 5; Tr. 153:3-8, 173:18-174:11.)

128. POSAs knew how to buffer transmucosal formulations of buprenorphine for this purpose. (Tr. 173:18-174:11.) For example, both Todd and Suboxone® include citric acid/sodium citrate buffers – the same buffers that are in Belbuca.® (DTX-174-003-004 at 2:21-3:4, Example 1, Example 17; DTX-172-0002, 0024; Tr. 153:25-154:10, 160:17-25, 173:18-174:2, 174:7-11, 694:3-23.) Just as BDSI did for Belbuca®, a POSA would have copied the acidifying buffers of Todd and Suboxone® in formulating Tapolsky's BEMA device for buprenorphine delivery. (Tr. 153:25-154:10, 160:17-25, 200:22-201:13.)

129. In view of the transmucosal formulations of Suboxone® and Todd, a POSA would have reasonably expected to use a citric acid/sodium citrate buffer in the polymeric diffusion environment of Tapolsky's device to maintain an acidic environment at the oral mucosa during bioerosion of the device. (Tr. 200:22-201:13.)

130. Todd would have provided a POSA with a reasonable expectation of successfully delivering buprenorphine from Tapolsky's device having a polymeric

diffusion environment buffered to an acidic pH of about 4, about 5, or about 6, and from a pH of about 4.5-5.5. (Tr. 174:12-175:2.)

131. The '866 and '843 patents describe several opioids that can be used in the invention, including fentanyl, buprenorphine, and butorphanol. (JTX-001 at 9:54-67; JTX-002 at 10:5-24; Tr. 683:4-684:18.)

132. Dr. Williams testified that the '866 and '843 patents provide sufficient direction for a POSA to determine the optimal pH range for any of the opioids disclosed, even though the patents do not include a specific pH teaching for any opioids other than buprenorphine and fentanyl. (JTX-001-0011 at 11:49-12:10; JTX-002-0013 at 12:5-33; Tr. 684:19-685:12, 685:16-686:10.)

C. Claims 4 and 5 of the '866 Patent Are Obvious

133. The time to first measurable concentration (i.e., T_{first}) in claim 4 and the duration of effective buprenorphine concentration in claim 5 are inherent properties of the device and dose administered as well as the sensitivity of the assay used to measure plasma concentration. (Tr. 327:12-328:12.)

134. In view of Bullingham I, a POSA would have reasonably expected achieving a T_{first} of about 45 minutes by administering buprenorphine in Tapolsky's BEMA device. (Tr. 343:16-344:1.)

135. A POSA would understand that buprenorphine can be administered using Tapolsky's BEMA device to maintain an effective concentration of at least 4 hours. (DTX-173 at Table 5; Tr. 346:2-14.)

136. The buprenorphine concentration-related parameters recited in claims 4 and 5 are not described in the '866 patent as providing any particular benefit, much less an unexpected result, when buprenorphine is administered transmucosally according to claim 1. (*See generally* JTX-001.)

137. In Table 4 of the '866 patent, the T_{first} for buprenorphine is 45 minutes for devices having a pH of 6 that are within the scope of claim 1 allegedly providing an enhanced uptake as well as devices having a pH of 7.25 that are outside the scope of claim 1. (JTX-001-0018 at 25:64-26:10.)

138. The '866 patent does not describe any benefit in maintaining buprenorphine concentrations effective for pain relief for at least 4 hours in contrast to shorter time periods. (JTX-001-0009 at 7:67-8:5.)

139. During prosecution, the Examiner specifically rejected claims 4-5 in several Office Actions. (JTX-004-0211-0213; JTX-004-0260-0262; JTX-0004-0303-0305.)

140. In response, BDSI did not separately argue patentability based on the limitations in these claims. (JTX-004-0231-0234; JTX-004-0281-0285; JTX-004-0315-0322; JTX-004-0330.)

D. There Are No Surprising or Unexpected Results

141. In a petition for accelerated examination in the '866 patent, BDSI told the PTO that Tapolsky does "not teach administration of an opioid" (JTX-004-0033.) This is incorrect. Tapolsky teaches the administration of the opioid butorphanol as suitable for use in the BEMA platform. (DTX-173 at [0053], Tr. 112:16-23, 693:1-694:2.) Butorphanol is also listed in the specification of the '866 patent. (JTX-001 9:54-10:6; Tr. 112:5-15.)

142. During prosecution of the '866 patent, BDSI submitted the Declaration of Dr. Andrew Finn signed September 12, 2011 (the "Finn Declaration"). (JTX-004-0231-36.)

143. The Finn Declaration states, "the devices which include a polymeric diffusion environment which is a buffered environment having a pH of between 4 and about 6 exhibit dramatically improved C_{max} and/or bioavailability as compared to devices having a polymeric diffusion environment at a pH of 7.25 or those having no buffered environment[.]" (JTX-004-0234.) Table 1 of the Finn Declaration sets forth the pharmacokinetic data for the devices that include a polymeric diffusion environment, and for Suboxone®:

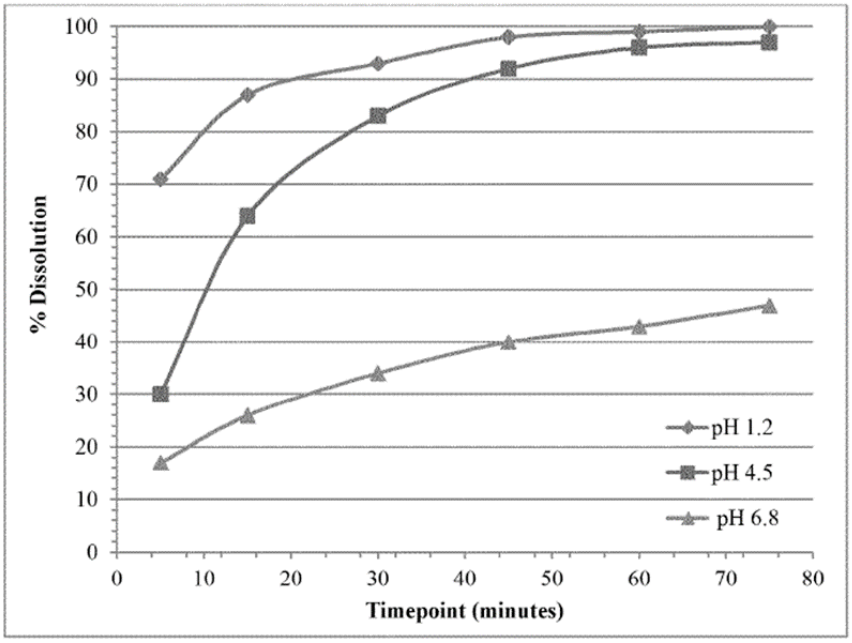
TABLE 1: Pharmacokinetics of Various Transmucosal Buprenorphine Devices								
DEVICE→	**Suboxone**	**BEMA 1**	**BEMA 2**	**BEMA 3**	**BEMA 4**	**BEMA 5**	**BEMA 6**	**BEMA 7**
pH→	**N/A**	**7.25**	**6.0**	**5.4**	**4.9**	**4.75**	**4.75**	**4.75**
DOSE→	2 mg	2 mg	2 mg	1 mg	1 mg	0.2 mg	0.5 mg	1.5 mg
T_{max} (hr)	1.96	3.00	3.10	2.19	2.31	2.88	2.31	2.25
C_{max} (ng/mL)	0.879	0.951	1.26	0.912	1.50	0.276	0.551	1.90
AUC_{inf} (hr*ng/mL)	8.582	10.77	11.20	5.856	9.396	2.005	4.399	16.33
Bioavail. (%) calc from AUC_{inf}	24.6	30.8	32.0	46.1	73.3	74.2	65.1	80.6

(JTX-004-0233-0234.)

144. The Finn Declaration states that the increased bioavailability at lower pH values was "unexpected and could not have been predicted from a mere change in pH [.]" (JTX-004-0234.)

145. Given that the solubility of buprenorphine was known to exponentially increase as pH drops from about 5 to about 4, and was lower at higher pH values, it was not surprising that the Cmax and bioavailability of buprenorphine would also increase for formulations in that pH range. (Tr. 182:14-183:17.) This is confirmed by a development report submitted to FDA in connection with the Belbuca® New Drug Application, which states, "[b]ased on buprenorphine pKa (8.5) and solubility data (solubility decreases as pH increases), the results for both film strengths in pH 6.8 dissolution media are low *as expected*." (DTX-024-0016; Tr. 687:17-688:14, 692:3-20) (emphasis added).

Figure 5: Dissolution of 900-µg Buprenorphine Film in Different pHs (1.2, 4.5, and 6.8)



Based on buprenorphine pKa (8.5) and solubility data (solubility decreases as pH increases), the results for both film strengths in pH 6.8 dissolution media are low as expected. The dissolution is somewhat faster at pH 1.2, especially at early time points compared to the results at pH 4.5. An acceptable dissolution profile was observed at early time points in pH 4.5 dissolution media and greater than 85% (Q+5%) release was achieved for both film strengths at 60 minutes. These results support the selection of pH 4.5 dissolution media for buprenorphine film.

146. The Finn Declaration states that Suboxone® was not buffered. (JTX-0004-233, Tr. 181:24-182:21.) However, Suboxone® contains a citric acid-sodium citrate buffer as also utilized in BEMA films. (JTX-0004-233, DTX-172-2; Tr. 153:25-154:10, 694:3-23, 698:6-699:17.) The Finn Declaration also incorrectly states that the pH of Suboxone® is "N/A". (JTX-0004-234, *see* DTX-365-003 at ¶¶ 4-5; Tr. 161:6-162:3; *see also* Tr. 695:19-696:2.)

147. In Table 1 of the Finn Declaration, the pH of the BEMA 1 formulation is listed as 7.25 and the pH of the BEMA 2 formulation is listed as 6.0. However, the actual pH of BEMA 1 was 6.8 and the actual pH of BEMA 2 is 5.3,

as confirmed by a document in BDSI's NDA for Belbuca® provided to FDA. (DTX-024-0006; Tr. 183:22-184:8, 192:12-193:7, 687:17-688:14.)

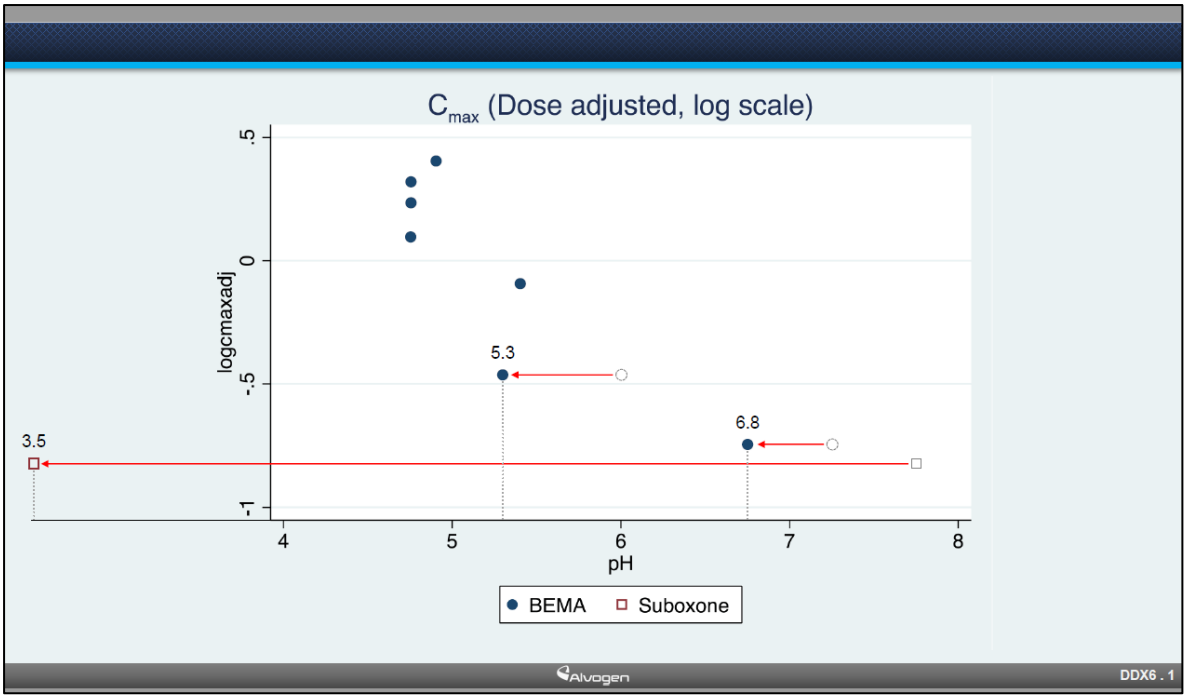
148. Dr. Williams testified that the developers of Belbuca® referred to the Cassidy reference when they were determining the solubility of buprenorphine. (Tr. 680:12-16.)

149. BEMA 1 and BEMA 2 were the only formulations tested prior to the filing date of the '866 patent and were discussed in Example 4 (with data presented in Table 4). The data for BEMA 3-7, as presented in the Finn Declaration, were generated after the filing date of the '866 patent. (JTX-004-0233; Tr. 183:18-21.)

150. The inventors of the '866 patent must have been aware of the pH dependent solubility of buprenorphine as taught by Cassidy, because otherwise they would have been unable to arrive at the lower limit of the claimed 4-6 pH range based on the data for BEMA 1 and BEMA 2 alone. (See Tr. 183:18-21.)

151. Dr. Thisted's analyses found no statistically significant difference between BEMA 1 and BEMA 2 with respect to Cmax or AUC, meaning that any difference between the two is plausibly attributable to chance. (Tr. 946:14-947:17.)

152. Demonstrative DDX6 (reproduced below) accurately depict how a graph of pH vs. Cmax would look with the correct pH values for BEMA 1, BEMA 2 and Suboxone®. (DDX6, *see* Tr. 948:21-24.)



The white dots indicate the data provided to the PTO for BEMA 1-2, and the red lines indicate that the actual pH values were lower, and the blue dots following the red lines indicate the actual pH values provided to FDA for BEMA 1-2. The blue square is the pH value for Suboxone® that Dr. Thisted inferred, and the red square is the actual pH value for Suboxone®. The remaining blue dots are for BEMA 3-7 as reported by Dr. Finn in his declaration.

153. During prosecution of the '843 patent, BDSI submitted the Declaration of Dr. Niraj Vasisht, signed March 23, 2017. (JTX-005-2769-776.)

154. During prosecution of the '866 patent, BDSI argued that the Todd reference relates primarily to the stability of aqueous buprenorphine solutions and that the solutions "may merely migrate to another aqueous solution, the saliva, while the solution is in the subjects mouth." (JTX-005-2771.) However, Todd

teaches sublingual delivery of buprenorphine, and discusses the "uptake of the drug" which refers to the passage of drug through the mucosa, i.e., absorption. (DTX-0174-0003 at 2:11-17; Tr. 175:1-2.)

IV. THE ASSERTED CLAIMS OF THE '539 PATENT ARE ANTICIPATED OR OBVIOUS

A. Scope and Content of the Prior Art[5]

155. The priority date of claims 9 and 20 of the '539 patent is December 21, 2012. (JTX-0003-0001.) All prior art described above with respect to the '866 and '843 patents is also prior art to the claims of the '539 patent.

1. Vasisht I (2008)

156. International Patent Publication WO 2008/0011194 A2 ("Vasisht I") (DTX-017) published on January 24, 2008 and is prior art to the '539 patent. (D.I. 249 at 3; DTX-017-0001; Tr. 205:4-11.)

157. Vasisht I is the publication of PCT Application PCT/US2007/016634, which is the PCT parent application to, and has the same specification as, the '866 and '843 patents. (DTX-017-0001, Tr. 292:19-25, 293:8-10; 371:4-9.)

[5] Vasisht I, Reder, and the other references cited in this section all published prior to December 21, 2011, the earliest possible filing date of the '539 patent. D.I. 249 at 3; DTX-017-001; DTX-078-001; DTX-077-001; DTX-177-001; DTX-170-0007; Tr. 88:17-89:2, 205:4-11, 216:19-21, 341:5-15, 401:13-23.

158. Vasisht I discloses BEMA devices and methods for the direct transmucosal administration of buprenorphine to provide enhanced uptake of buprenorphine. (D.I. 249 at 3; DTX-017 at [0004], [0010], [0011], [0024], [0037], [0041], [0045]; Tr. 211:23-212:16; 241:13-20.)

159. Vasisht I discloses that the use of the buprenorphine-containing devices are effective to treat "any pain known in the art, caused by any disease, disorder, condition, and/or circumstance." (DTX-017-0013-0014 at [0045]; Tr. 214:24-215:14.)

160. Vasisht I discloses examples of pain, including moderate to severe pain, chronic pain, or lower back pain, for which treatment with the buprenorphine-containing devices is effective. (DTX-017 at [0011], [0029], [0041], [0045]; Tr. 211:23-212:16, 212:17-24, 213:18-22, 214:24-215:25.)

161. Vasisht I discloses that the devices may be administered "at dosages and for periods of time effective for treatment of a subject" and in "[d]osage regimens . . . adjusted to provide the optimum therapeutic response." (DTX-017-0011 at [0036]; Tr. 212:17-24.)

162. Vasisht I discloses that "several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation." (DTX-017-0011 at [0036]; Tr. 212:17-24.)

163. Vasisht I discloses that a transmucosal drug delivery device containing buprenorphine may be administered at dosages and for periods of time effective for treatment of a subject. (D.I. 249 at 4; DTX-017-0011 at [0036]; Tr. 212:17-24.)

164. Vasisht I teaches that the device containing buprenorphine provides a therapeutically effective total daily dose of buprenorphine such that pain, including chronic pain, is treated and/or alleviated. (DTX-017 at [0011], [0036], [0041], [0045]; Tr. 211:23-212:24, 213:18-22, 214:24-215:25.)

165. Vasisht I discloses a bioerodable mucoadhesive layer including an effective amount of buprenorphine in a polymeric diffusion environment. (DTX-017 at [0012], [0019], [0024], [0048], [0049], [0052], [0060], [0072], [0100], [0120]; Tr. 212:25-213:9.)

166. Vasisht I discloses a BEMA device containing buprenorphine that includes a polymeric diffusion environment buffered to a pH of between about 4 and about 6, including between about 4.5 and about 5. (D.I. 249 at 3; DTX-017 at [0012], [0016], [0019], [0024], [0048], [0049], [0052], [0060], [0072], [0100], [0120], [0121]; Tr. 212:25-213:9, 240:13-19, 241:23-242:12.)

167. Vasisht I discloses that a BEMA device including buprenorphine may include buprenorphine in an amount from about 25, 50, 75, 100, 150, 200,

300, 400, 500, 600, 700, 900, 1000, 1200, 1500, 1600, or 2000 mcg.[6] (D.I. 249 at 4; DTX-017-0015-0016 at [0052]; Tr. 212:25-213:9; 373:18-374:10.)

168. Vasisht I further discloses that buprenorphine Cmax is dose proportional such that Cmax varies linearly with the dose administered. (DTX-017-0017-0018 at [0057]; Tr. 216:1-216:18, 325:25-326:10; 373:10-374:21.)

169. Vasisht I discloses a BEMA device that includes a backing layer that provides a unidirectional gradient on application to a mucosal surface, for rapid and efficient delivery of buprenorphine. (D.I. 249 at 3; DTX-017 at [0010]-[0013], [0018]-[0019], [0024], [0034], [0040], [0047], [0073], [0077], [0099]; Tr. 239:21-240:12, 242:13-243:4.)

170. Vasisht I describes a method of preparing a buffered backing layer for the claimed devices, including a recitation of the components of the backing layer used, and the wet weight percentages of each ingredient. (DTX-017 at [0014], Example 1, [0099]; Tr. 206:3-11.) The components listed do not include an opioid antagonist.

171. Vasisht I discloses a backing layer formulation that includes the following components by weight percent converted to dry basis: sodium benzoate (0.5 wt.%), methylparaben (0.5 wt.%), propylparaben (0.1 wt.%), citric acid (0.5

[6] Microgram, or "mcg," is used interchangeably herein and in the prior art as "µg." One milligram ("mg") equals 1000 µg.

wt.%), vitamin E acetate (0.05 wt.%), sodium saccharin (0.5 wt.%), hydroxypropyl cellulose (63 wt.%), hydroxyethyl cellulose (32%), titanium dioxide (2.7%), peppermint oil (0.9 wt.%). (DTX-017-0028-0030 at Example 1, [0099]; Tr. 206:5-207:23, 209:20-210:3, 213:10-17; DDX4.31.)

172. Vasisht I discloses that the subject treated may be "opioid tolerant" and/or to treat subjects "already on chronic opioid therapy." (DTX-017-0013-0014 at [0043], [0045]; Tr. 214:4-8.)

173. Vasisht I discloses that the subject treated is "opioid-experienced," as this Court construes the term. (DTX-017-0013-0014 at [0043], [0045]; Tr. 214:4-8; D.I. 114.)

174. Vasisht I discloses that the transmucosal drug delivery device containing buprenorphine can be administered to opioid-experienced subjects currently receiving opioid therapy. (DTX-017-0013-0014 at [0043], [0045]; Tr. 214:4-8.)

175. Vasisht I discloses that any side effects experienced by subjects treated with the devices are "mild or moderate in nature." (DTX-017-0036 at [0118]; Tr. 204:13-19, 214:9-19, 371:10-373:9, 399:16-400:8, 399:20-400:8.)

176. Vasisht I discloses that subjects treated with the devices experience "little or no constipation." (DTX-017-0017 at [0055]; Tr. 214:8-19; 371:10-373:9; 400:9-401:12.)

2. Reder (2001)

177. U.S. Patent No. 6,231,886 ("Reder") (DTX-078) published on May 15, 2001 and is prior art to the '539 patent. (DTX-078-1; Tr. 216:19-21.)

178. Reder is directed to buprenorphine drug delivery devices "which allow[] for reduced plasma concentrations of buprenorphine over a prolonged time period than possible according to prior art methods, while still providing effective pain management." (DTX-078-0008 at 2:63-67; Tr. 222:22-223:13, 374:22-375:11.)

179. Reder discloses a mean Cmax of 184.89 pg/mL (equivalent to 0.185 ng/mL) following administration of a transdermal device including buprenorphine that was effective to treat pain in that subject. (DTX-078-0020 at Table 2; Tr. 223:14-22, 375:1-376:2.)

180. Reder's reported mean Cmax of 0.185 ng/mL is within the claimed range of "about 0.156 ng/mL to about 0.364 ng/mL." (JTX-0003 at Claim 9; DTX-078-0020 at Table 2; Tr. 395:25-396:21.)

181. Reder discloses, "[a]ny mode of [administration] may be utilized" to obtain the desired plasma concentrations of buprenorphine. (DTX-078 at 3:56-59; Tr. 223:23-224:4, 224:13-20.)

182. Reder discloses, "[f]or example, the buprenorphine may be administered transdermally, parenterally, sublingually, orally, buccally, rectally, etc." (DTX-078-0009 at 3:56-59; Tr. 223:23-224:4, 224:13-20.)

3. Bullingham I (1981)

183. Bullingham I published in 1981 and is prior art to the '539 patent. (DTX-077-0001, Tr. 88:18-89:13.) The discussion of Bullingham I set forth in Section III.A.2.(b) *supra* is incorporated by reference herein.

184. Bullingham I is a peer-reviewed study involving the administration of buprenorphine sublingual tablets at a total dose of 400 mcg. (DTX-077-0001-0002; Tr. 332:10-333:10.)

185. Bullingham I describes the pharmacokinetic and pharmacodynamic results of the administration of sublingual buprenorphine tablets. (DTX-077-0001; Tr. 88:18-89:13, 332:23-333:14.) The sublingual dose was preceded by administration of 300 mcg of intravenous buprenorphine. (DTX-077-0001-0002; Tr. 332:23-333:14.) The contribution of the intravenous dose to measured concentrations of buprenorphine in the blood was removed from the results by "stripping." (DTX-077-0002; Tr. 333:15-334:7.)

186. Bullingham I teaches that the Cmax resulting from administration of 400-mcg of sublingual buprenorphine was 0.74 +/- 0.16 ng/mL. (DTX-077-0003 at Table 2; Tr. 397:9-23.)

4. Bullingham II (1982)

187. Bullingham II published in 1982 and is prior art to the '539 patent. (DTX-177-0001; Tr. 341:5-342:5, 397:9-23.)

188. Bullingham II presents the results of a nearly identical, larger study of the same design as Bullingham I in 15 patients and included sublingual buprenorphine tablet doses of 400 mcg and 800 mcg. (DTX-177-0001; Tr. 341:5-342:5.) As was done in Bullingham I, the concentrations from the IV dose were subtracted from the analysis, and Bullingham II reports the concentrations from the second, sublingual dose. (Tr. 342:6-12.)

189. Bullingham II discloses a C_{max} of 0.5 +/- 0.06 ng/mL for a 400-mcg dose of sublingual buprenorphine, and 1.04 +/- 0.27 ng/mL for a dose of 800-mcg. (DTX-177-0001, -0008 at Table 7; Tr. 397:9-23.)

5. Temgesic® (2008)

190. Temgesic® published on May 9, 2008 and is prior art the '539 patent. (DTX-170-0007; Tr. 401:13-402:12.) Temgesic® has been available since the early 1980s and was the sublingual buprenorphine tablet product used in the studies of Bullingham I and Bullingham II. (Tr. 397:9-17, 401:16-23.)

191. Temgesic® describes sublingual tablets containing 216-mcg buprenorphine. (DTX-170-0001.)

192. Temgesic® is a "[s]trong analgesic" indicated for the treatment of pain. (DTX-170-0003.)

193. Temgesic® discloses that "less than 1% of patients" treated with Temgesic® experienced constipation as an "[a]dverse reaction[]." (DTX-170-0005; Tr. 401:13-402:12.)

B. Claim 9 is Anticipated or Obvious and Claim 20 is Obvious

194. Vasisht I discloses a method of treating moderate to severe chronic low back pain (as required by claim 9), and a method of treating chronic pain (as required by claim 20). (JTX-0003-0015-0016 at Claims 9, 1; DTX-017 at [0004], [0010], [0011], [0024], [0029], [0037], [0041], [0045]; Tr. 211:23-212:24, 213:18-22, 214:24-215:25, 241:13-20.)

195. Vasisht I teaches the "once or twice daily" administration of "a mucoadhesive bioerodable drug delivery device to the oral mucosal surface of the subject" "in need thereof." (JTX-0003-0015-0016 at Claims 9, 1; DTX-017 at [0010], [0036]; Tr. 212:17-24.)

196. Vasisht I teaches a device comprising "a bioerodable mucoadhesive layer comprising an effective amount of buprenorphine disposed in a buffered polymeric diffusion environment, wherein the polymeric diffusion environment is a buffered environment having a pH of between about 4 and about 6." (JTX-0003 at Claims 9, 20; DTX-017 at [0024], [0052], [0072], [0019], [0048], [0049],

[0012], [0060], [0064], [0100], [0120]; Tr. 212:25-213:9.) Vasisht I teaches that the amount of buprenorphine included in the bioerodable mucoadhesive layer may be between "about 100 [mcg] and about 0.9 mg." (JTX-0003-0015 at Claim 1; DTX-017-0017-0018 at [0057]; Tr. 216:1-17, 373:10-374:21.)

197. Vasisht I teaches administration of a "total daily dose of buprenorphine" that "is effective for treating moderate to severe chronic low back pain." (JTX-0003-0015-0016 at Claim 9; DTX-017 at [0036], [0011], [0041], [0045]; Tr. 211:23-212:24, 213:18-22, 214:24-215:25.)

198. Vasisht I teaches a method "wherein the subject is an opioid-experienced subject." (JTX-0003-0015-0016 at Claim 9, Claim 20; DTX-017 at [0043], [0045]; Tr. 214:4-18; D.I. 114.)

199. Vasisht I teaches a method "wherein the subject treated experiences mild or moderate common opioid adverse effects, or no common opioid adverse effects." (JTX-0003-0015-0016 at Claim 9, Claim 20; DTX-017 at [0055], [0118]; Tr. 204:13-19, 214:9-19, 371:10-373:9, 399:20-400:8.)

200. Claims 9 and 20 further require that the backing layer is buffered to a pH between about 4.0 and about 4.8 and does not include an opioid antagonist. JTX-003-0015-0016 at Claim 9, Claim 20. Vasisht I discloses a method of preparing a backing layer for the claimed devices, including a recitation of the components of the backing layer used, and the wet weight percentages of each

ingredient. (DTX-017 at [0014], Example 1, [0099]; Tr. 206:3-207:23, 209:20-210:3, 213:10-17; DDX4.31.)

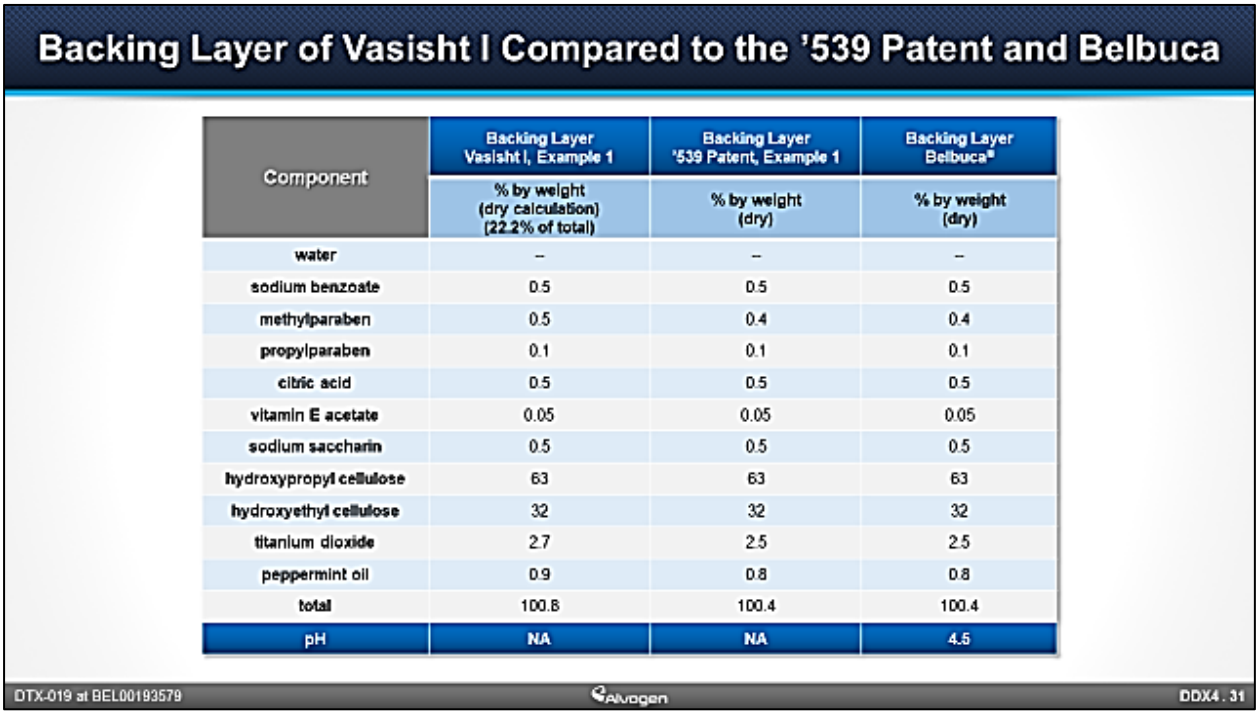
201. Example 1 of the '539 patent recites a method of preparing a backing layer for the devices to be used in the claimed method, including a recitation of the components of the backing layer used, and a dry weight percentage of each ingredient. (JTX-003-0012 at Example 1, 10:9-27; Tr. 206:12-207:23.) The listed ingredients for the backing layer formulations in Vasisht I and Example 1 of the '539 patent are the same. (JTX-003-0012 at Example 1, 10:9-27; DTX-017-0028-0030 at Example 1, [0099]; Tr. 206:3-207:23; DDX4.31.)

202. The weight percentages of the ingredients in the example backing layer of Vasisht I and the backing layer disclosed in the '539 patent are materially identical for most components. (Tr. 206:12-207:23; DDX4.31.) While the two formulations slightly differ with respect to the proportions of peppermint oil and titanium dioxide, a POSA would have known that peppermint oil (flavoring agent) and titanium dioxide (coloring agent), as ingredients in the backing layer formulation, would not affect the pH of the layer. (*See* DTX-019-0023; Tr. 207:6-16; DDX4.31.)

203. A POSA would have known that the pH of the backing layer disclosed in Vasisht I would have inherently been the same as that disclosed in Example 1 of the '539 patent. (Tr. 206:12-207:23 at 207:17-23.)

204. Belbuca® includes a backing layer having a pH of 4.5. (Tr. 207:17-23, 574:13-576:25 at 574:13-21, 575:24-576:8, 576:16-576:25.) This pH data was obtained from the same backing layer formulation as that reported to the FDA as part of the Belbuca® NDA. (Tr. 575:13-576:8.)

205. According to BDSI's internal documents, the backing layer composition for the commercial formulations of Belbuca®, referred to as F14 and F24, are identical in components and proportions to the backing layer disclosed in the '539 patent. (JTX-003-0012 at Example 1; *see* DTX-019-0041, -0044, and -0045 (Table 21) (describing the backing layer for the final formulations of Belbuca®, F14 and F24); Tr. 206:12-209:17; DDX4.31.)



Component	Backing Layer Vasisht I, Example 1	Backing Layer '539 Patent, Example 1	Backing Layer Belbuca®
	% by weight (dry calculation) (22.2% of total)	% by weight (dry)	% by weight (dry)
water	–	–	–
sodium benzoate	0.5	0.5	0.5
methylparaben	0.5	0.4	0.4
propylparaben	0.1	0.1	0.1
citric acid	0.5	0.5	0.5
vitamin E acetate	0.05	0.05	0.05
sodium saccharin	0.5	0.5	0.5
hydroxypropyl cellulose	63	63	63
hydroxyethyl cellulose	32	32	32
titanium dioxide	2.7	2.5	2.5
peppermint oil	0.9	0.8	0.8
total	100.8	100.4	100.4
pH	NA	NA	4.5

206. The backing layer composition for the commercial formulations of Belbuca® are therefore materially identical to the backing layer composition disclosed in Vasisht I. (DTX-017 at Example 1; DTX-019-0045 at Table 21; Tr. 206:12-209:17.)

207. A POSA would have known that the backing layer disclosed by Vasisht I has the same pH (4.5) as does the backing layer described in the '539 patent and included in Belbuca®. (Tr. 207:17-23, 209:10-210:3.) A pH of 4.5 is within the claimed range of "about 4.0 to about 4.8." (Tr. 209:10-210:3.)

208. During prosecution of the '539 patent, the PTO repeatedly rejected the claims over Vasisht I. (JTX-0006-0075-0081, JTX-0006-0157-0167, JTX-0006-0193-0204, JTX-0006-0233-0256, JTX-0006-3790-3806, JTX-0006-4043-4063, JTX-0006-4116-4132.) Following one such rejection, Dr. Vasisht submitted a declaration stating, "we did recently remake the backer formulation" described in Vasisht I, and purportedly measured the pH of that formulation to be, on average, 5.61. (JTX-0006-4100-4102 at JTX-006-4101; Tr. 210:8-211:6.) The measurements Dr. Vasisht reported cannot have been accurate in view of the similarities between the backing layer formulation of Vasisht I and that of the '539 patent and Belbuca®. (JTX-0006-4101, Tr. 210:4-211:22.)

209. A POSA would have been motivated to incorporate the backing layer described by Vasisht I into a device including buprenorphine in the

mucoadhesive layer instead of fentanyl, which is recited in Vasisht I. (DTX-017-0029 at [0099].) Vasisht I recites an example of such a preparation, stating that "[d]evices containing buprenorphine were also produced using the same method as described in Example 1, except that buprenorphine was added to the mucoadhesive polymeric diffusion environment instead of fentanyl citrate." (DTX-017-0037 at Example 3, [0120].) Vasisht I thus provides explicit teaching that buprenorphine and fentanyl are interchangeable for treating pain in the methods described.

210. Claim 20 requires that "between about 1.5%-8.5% of subjects treated experience constipation as a [treatment emergent adverse event] TEAE". (JTX-0003 at Claim 20; Tr. 400:9-17.) This limitation was added during prosecution (*see* JTX-0006-0217), but was never relied-upon in any subsequent argument by the applicants as patentable independent of claim 1. (JTX-0006-2319-2322; JTX-0006-3836-3844; JTX-0006-4091-4099; JTX-0006-4141-4149).

211. The prior art Vasisht I and Temgesic® teach that low incidences of constipation were known to be associated with transmucosal administration of buprenorphine. (DTX-017-0017 at [0055] (treatment the device of the present invention causes "little or no constipation"); Tr. 214:8-19, 371:10-373:9, 400:9-401:2 at 400:18-23; DTX-170-0005 (transmucosal, sublingual administration of buprenorphine results in "less than 1%" of subjects experiencing constipation); Tr. 401:13-402:12.)

212. A POSA would further have expected that 5-10 percent of patients on chronic opioid therapy experience constipation as a side effect, which overlaps with the claimed range. (Tr. 401:3-13.) A POSA would also have understood that side effects like constipation are the result of buprenorphine and the dosage amount, and not the drug delivery system. (Tr. 501:25-503:13 at 503:6-13.)

213. Asserted claim 20 also requires that the device provides, "a steady-state Cmax of plasma buprenorphine in a range between about 0.156 and about 0.364 ng/mL."[7] (JTX-0003-0015 at Claim 1; Tr. 213:23-214:3, 373:10-17.)

214. Cmax is a pharmacokinetic parameter that refers to "the maximum plasma concentration of a drug following administration." (Tr. 325:7-11.) "Cmax depends on the drug, on the device, and on the dose." (Tr. 325:16-19.) Steady-state Cmax refers to the Cmax observed when repeated doses of the drug are administered, and thus further "depends on the dosing interval." (Tr. 326:22-327:11.) Steady-state Cmax is a pharmacokinetic parameter that depends on a given dose, in a given device, over a given dosing interval. (Tr. 326:22-327:11.)

215. A POSA would have been motivated to use the method and device taught by Vasisht I to achieve a steady-state Cmax in the claimed range as taught by Reder with a reasonable expectation of success. (Tr. 224:13-20, 375:12-376:2,

[7] A "nanogram" or "ng" is one billionth of a gram and a "milliliter" ("mL") is one thousandth of a liter.

395:25-397:8 at 396:14-17.) Vasisht I discloses buprenorphine, the claimed BEMA device, the claimed dosage range, the dosing interval, and the dose proportionality of buprenorphine. Section IV.A.1 *supra*. Reder teaches a buprenorphine Cmax of 0.185 ng/mL, squarely within the claimed range, that is associated with effective pain management. (DTX-078-0020 at Table 2; Tr. 223:14-22, 375:12-376:10, 395:25-397:8.) A POSA in view of Reder would have understood that a concentration 0.185 ng/mL would provide effective pain relief. (Tr. 375:21-376:2, 396:18-21.) A POSA would have understood, in view of Reder's disclosure that the transdermal device releases buprenorphine over several days, that the Cmax of 0.185 ng/mL in Table 2 would be a steady-state value. (DTX-078-0019-0020 at Example 1 (24:46-49, 26:10-19); Tr. 375:12-376:2, 395:25-397:8.)

216. Vasisht I discloses a wide range of buprenorphine doses spanning about two orders of magnitude from 25 mcg to 2000 mcg. (DTX-017 at [0052], Tr. 374:2-10). Some of these doses are too high to achieve a Cmax within the claimed two-fold range of Cmax values. (Tr. 373:18-374:21.)

217. A POSA would understand Vasisht I's drug delivery device could be configured to provide the steady-state Cmax taught by Reder in order to effectively treat chronic pain. (Tr. 395:25-397:1.)

218. A POSA would have understood that both Vasisht I and Reder taught that buprenorphine may be effectively administered to treat or manage pain. (DTX-017-0013-0014 at [0045]; Tr. 214:24-215:14; DTX-078-0008 at 2:63-67; Tr. 222:22-223:13, 374:22-375:11.)

219. A POSA would have understood that the critical disclosure in Reder is a buprenorphine Cmax within the claimed range that is effective to treat pain, not the particular route of administration. (Tr. 375:21-376:10, 377:23-378:20.)

220. A POSA further would have understood that Reder's disclosure is not restricted to transdermal delivery devices, and provides guidance relevant to transmucosal devices, for example, as taught by Vasisht I. (DTX-078-0009 at 3:56-59, Tr. 223:23-224:6; 224:13-20.) Reder explicitly discloses that "[a]ny mode of [administration] may be utilized," including "buccal[]" administration. (DTX-078-0009 at 3:56-59, Tr. 223:23-224:6; 224:13-20.)

221. A POSA would have understood that the delivery mechanism itself is not relevant to whether the resulting blood concentrations are associated with effective pain relief. (Tr. 376:3-10, 376:25-377:2, 377:8-15, 377:21-379:8.)

222. A POSA further would have understood that Reder's disclosure is not restricted to transdermal devices, and provides guidance relevant to transmucosal devices, for example, as taught by Vasisht I. Reder explicitly discloses that "[a]ny mode of [administration] may be utilized," including

"buccal[]" administration. (DTX-078-0009 at 3:56-59; Tr. 223:23-224:6; 224:13-20.)

223. A POSA would have been motivated, with a reasonable expectation of success, to select doses of buprenorphine, as taught by Vasisht I, for use in the device of Vasisht I to provide a Cmax within the claimed range, as taught by Reder. (DTX-017 at [0052], [0057]; DTX-078-0020 at Table 2; Tr. 373:10-375:2, 395:25-397:1.)

224. As discussed above, Bullingham I and Bullingham II recite the Cmax resulting from transmucosal administration of buprenorphine at 400-mcg and 800-mcg dosages. (DTX-077-001; DTX-177-001; Tr. 397:9-23.) Although the Cmax values disclosed in Bullingham I and Bullingham II are higher than those in the claimed range, a POSA would have used those values to calculate a mean buprenorphine Cmax/mcg of 0.0015 ng/mL. (Tr. 397:18-396:9, DDX3.66.)

Bullingham I and Bullingham II Teach C_{max} for Buprenorphine

SUBLINGUAL BUPRENORPHINE USED POSTOPERATIVELY: TEN HOUR PLASMA DRUG CONCENTRATION ANALYSIS

R.E.S. BULLINGHAM, H.J. McQUAY, E.I.B. PORTER, M.C. ALLEN & R.A. MOORE

Defendants' Exhibit DTX 177

DTX-177-0001

ALVB021835

	Dose	C_{max}	SD	Per mcg	SD per mcg
Bullingham I	400 mcg	0.74	0.16	0.00185	0.0004
Bullingham II	400 mcg	0.50	0.06	0.00125	0.00015
Bullingham II	800 mcg	1.04	0.27	0.0013	0.000338

Mean C_{max} per mcg	**0.0015**
Mean SD per mcg	0.0003
Lower	0.0012
Upper	0.0018

DTX 177 Alvogen DDX3 . 66

225. A POSA would have selected a dose from those recited in Vasisht I that would produce the desired Cmax, i.e., within the claimed range. (Tr. 397:24-399:14.) For example, using the per-microgram Cmax calculated above, a dose of 200-mcg, as recited in Vasisht I, would produce a Cmax of about 0.29 ng/mL. (Tr. 398:10-399:9.)

226. A POSA would have understood that a Cmax calculated based on Bullingham's values would not have been consequentially different from a steady-state Cmax. (Tr. 399:6-15.)

C. No Evidence of Unexpected Results

227. BDSI's expert Dr. Taft testified, "changing" or "lower[ing]" the pH of the backing layer resulted in an increase of bioavailability, but he nowhere

testified what the pH for the backing layer should be changed (or lowered) to be in order to obtain such an increase. (Tr. 804:2-806:19 at 804:9-804:13, 805:14-18.)

228. BDSI has not provided any evidence that any improved bioavailability is provided by backing layers having a pH encompassed by the claims. BDSI relies on data from confidential, non-public BDSI and Endo documents that discuss the testing of different backing layer formulations (identified as "F1," "F2," "M1," and "M2") that either included or did not include citric acid. (Tr. 804:17-805:7; 805:22-806:2). No pH information is provided for any of these tested formulations.

229. The prior art, particularly Vasisht I, discloses the use of citric acid in the backing layer of the device. (DTX-017-0029 at [0099]; Tr. 844:13-845:22.) As discussed above in Section IV.B *supra*, Vasisht I also discloses that the backing layer has substantially the same composition as the example provided by the '539 patent, and has a pH of 4.5, within the claimed range. (Tr. 206:3-210:3.)

230. BDSI provides no comparison of the components or properties of the device described in the '539 patent relative to the device described in Vasisht I.

231. Any purported unexpected properties provided by the backing layer encompassed by claims 9 and 20 of the '539 patent would have also been provided by the backing layer disclosed in Vasisht I. (*See* Tr. 139:15-141:5 (defining and discussing bioavailability); 206:3-210:3.)

232. U.S. Patent Publication US2009/0264385 ("Crowley"), published on October 22, 2009, discloses the use of citric acid to lower the pH of the backing layer of a drug delivery device, and further discloses that modifying the pH of the backing layer can be used to control the behavior of the device. (DTX-179 at [0002], [0134]; Tr. 224:21-226:9.)

233. U.S. Patent Publication US2004/0180080 ("Furusawa") teaches that the pH of the layers of a disintegrating drug delivery device influence the characteristics of the layers and overall device. (DTX-187-0015 at [0099]; Tr. 226:10-227:8.)

234. A POSA would have expected, in view of the general prior art, that modification of the pH of the backing layer in the claimed drug delivery device, for example, by inclusion of citric acid, would be expected to alter the device's behavior. (Tr. 226:19-228:7, 228:8-229:6.)

V. THERE WAS NO LONG-FELT NEED

235. The asserted claims do not mention addiction, abuse or misuse (Tr. 499:15-17); risk of respiratory depression or buprenorphine's ceiling effect (Tr. 501:21-24); the risk of prolongation of the QT interval (Tr. 506:5-7); and make no mention of either DEA scheduling or ease of prescribing (Tr. 490:20-491:1.)

236. With respect to addiction, abuse or misuse, there is no difference between administration by transdermal or buccal routes. (Tr. 497:18-21.) With respect to respiratory depression and buprenorphine's ceiling effect, the effects of buprenorphine are the same irrespective of how it is administered, including between Butrans® (transdermal) and Belbuca® (buccal). (Tr. 501:12-15.) The risk associated with QT prolongation is a function of buprenorphine, not the route of administration. (Tr. 506:2-4.) The risk of adverse events for Belbuca® is similar to the risk associated with Butrans®, are typical for an opioid, and are the result of the properties of the buprenorphine itself. (Tr. 501:25-503:13.)

237. Drugs can be reclassified by DEA due to changing circumstances; for example, hydrocodone was a Schedule III for decades, but was recently re-classified as a schedule II. (Tr. 488:9-18.)

238. Buprenorphine was classified as a schedule II opioid in 1981 and was re-classified as a schedule III opioid in 2002. (JTX-471-0003; Tr. 480:10-17.)

239. As of the early to mid-2000s, Dr. Fine testified that he and others of the field began becoming concerned regarding the number of opioid related fatal poisonings, and became aware that the prescription opioids were starting to fall into the category of substance abuse, misuse and diversion. (Tr. 548:13-549:12.)

240. The earliest documentary evidence in the record that points to the opioid crisis was a NCHS Data Brief that was published in September 2009. (JTX-

410-0002; Tr. 930:19-932:8.) The Data Brief highlights trends in fatal opioid analgesic-related poisonings from the years 1999-2006. (JTX-410-0001.)

241. Dr. Rauck testified that although Belbuca® has been on the market since 2016, the opioid crisis continues, and Belbuca® did not solve the opioid crisis. (Tr. 904:5-905:1.) Dr. Rauck concedes that despite the introduction of Belbuca®, there is still a need for chronic pain treatment with a lesser potential of addiction, abuse and misuse, stating, "there continues to be an unmet need, absolutely." (Tr. 910:4-9.) Dr. Rauck's implies that the need may be met by "some really exciting, novel, non-opioid analgesics that would hopefully get away from all of this." (Tr. 910:4-9.)

242. The Belbuca® product label contains a "Black Box Warning," which is the highest level of warning required by FDA on drug labels. (JTX-233-0001; Tr. 495:14-20, 496:9-13.)

243. The Belbuca® label states: "BELBUCA exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess a patient's risk before prescribing and monitor regularly for these behaviors and conditions." (JTX-233-0001; Tr. 496:25-497:17, 498:11-499:10.)

244. The Belbuca® label states, "Misuse or abuse of BELBUCA by chewing, swallowing, snorting or injecting buprenorphine extracted from the

buccal film will result in the uncontrolled delivery of buprenorphine and pose a significant risk of overdose and death." (JTX-233-3.)

245. The Belbuca® label states "Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients on proper administration of BELBUCA to reduce risk." (JTX-233-0001; Tr. 499:18-500:19.)

246. The Belbuca® label states, under "Warnings and Precautions": "Risk of Prolonged QTc Interval: Avoid in patients with Long QT syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic medications." (JTX-233-0001; Tr. 504:24-506:1, 910:25-911:6.)

247. The Belbuca® label states: "Do not exceed a dose of BELBUCA 900 mcg every 12 hours due to the potential for QTc interval prolongation." (JTX-233-0005; Tr. 915:2-915:16, 916:12-16.)

248. The Belbuca® label states under "Adverse Reactions "Most common adverse reactions (>5%) include: nausea, constipation, headache, vomiting, dizziness, and somnolence." (JTX-233-0001; Tr. 501:25-502:21.)

249. The Butrans® label also contains a "Black Box Warning." (DTX-115-0001, Tr. 497:19-498:2.)

250. The Butrans® label states: "BUTRANS exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess a

patient's risk before prescribing and monitor regularly for these behaviors and conditions." (DTX-115-0001; Tr. 498:11-499:10.)

251. The Butrans® label states: "Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients on proper administration of Butrans to reduce risk." (DTX-115-0001; Tr. 497:22-498:19.)

252. The Butrans® label states, under "Warnings and Precautions": "Avoid in patients with Long QT syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic medications." (DTX-115-0001; Tr. 504:24-506:1, 910:25-911:6.)

253. The Butrans® label states under "Adverse Reactions "Most common adverse reactions (>5%) include: nausea, headache, application site pruritus, dizziness, constipation, somnolence, vomiting, application site erythema, dry mouth, and application site rash." (DTX-115-0001; see also JTX-417-0001; Tr. 502:22-503:13.)

254. Mr. Guy Donatiello testified as the corporate representative of Endo Pharmaceuticals, regarding the relationship between Endo Pharmaceuticals and BDSI with respect to the patents-in-suit and Belbuca®, contracts, licenses or other agreements concerning the patents-in-suit and Belbuca®, any assessments regarding the commercial or medical need for Belbuca®, and the basis for Endo's

decision to discontinue development and/or commercialization of Belbuca®. (Tr. 464:6-10; DTX-038-0050-0052.)

255. Effective January 25, 2012, Endo entered into a license and development agreement with BDSI regarding Belbuca® in which Endo obtained a license to develop, use, commercialize, distribute and sell Belbuca®. (Tr. 465:24-466:10; JTX-357-0002; *see* Tr. 475:10-19) Under the terms of the agreement, Endo agreed to pay BDSI an upfront payment of 30 million dollars, tens of millions of dollars in the form of milestone payments, as well as product royalties. (JTX-0357-0030-33; *see* Tr. 475:10-19.)

256. Endo sought priority review from FDA in connection with the NDA for Belbuca®, contending that the drug satisfied and unmet medical need. The request was denied because there was already a Schedule III buprenorphine product available (Butrans®) and Endo had failed to provide evidence that Belbuca® would represent a significant improvement over existing therapies. (Tr. 507:12-509:4; DTX-112-0004.)

257. Following launch, sales of Belbuca® lagged behind Endo's goal. (Tr. 467:11-19; DTX-043-0003.) According to Endo internal meeting minutes, as of June 2016, the unmet need that Belbuca® was trying own was not defined in the marketplace. Endo's corporate representative interpreted this statement as

indicating, "people aren't aware of the unmet need that Belbuca® is trying to address." (Tr. 467:20-468:14; DTX-044-0002.)

258. By December 2016, Endo had made the decision to return Belbuca® to BDSI. (Tr. 468:15-470:3; JTX-0358-0001.) Endo's corporate representative testified that the reason for returning Belbuca® to BDSI was that Endo intended to get out of the business of promoting branded opioids. (Tr. 470:4-471:1.)

259. Endo continued to sell its oxymorphone opioid product Opana® until summer of 2018, at which time it withdrew the product from the market due to FDA pressure. (Tr. 560:7-22). Endo still sells the opioid analgesic Percocet, which is currently listed on its website. (Tr. 492:11-25, 555:16-556:1.)

260. Dr. Fine and his colleagues do not prescribe Belbuca® because there are hosts of other drugs, including other opioids, which are sufficient for their patients. These include the opioids morphine, oxymorphone, oxycodone, hydromorphone, methadone, hydrocodone, fentanyl, Tramadol and Tapentadol. (Tr. 491:2-491:16.)

261. Dr. Rauck has been retained as a consultant by BDSI independent of his work on this case. (Tr. 898:17-20.) Dr. Rauck helped design and implement the Belbuca® clinical trials. (Tr. 900:20-23.) Dr. Rauck is also a member of the Speakers' Bureau for BDSI to market drugs to other doctors. (Tr. 900:24-901:13.) BDSI hired Dr. Rauck to promote Belbuca®. (Tr. 901:14-20.) In connection with

his role as a consultant for BDSI, Dr. Rauck has received confidential information that he could not share with competitors. (Tr. 900:16-19.) BDSI provides materials for Dr. Rauck's presentations when he has acts on their behalf, and BDSI pays Dr. Rauck when he acts as a speaker on their behalf. (Tr. 902:20-903:1.)

262. Dr. Rauck prescribes opioids to 70 to 80% of his patients. (Tr. 905:2-905:4.) Of those patients on opioids, Dr. Rauck prescribes Belbuca® 25% of the time, and other opioids 75% of the time. (Tr. 905:5-905:11.) Up to half of all of Dr. Rauck's patients are prescribed Schedule II drugs. (Tr. 905:15-18.) Dr. Rauck currently prescribes fentanyl, hydromorphone, oxymorphone, morphine, oxycodone, and hydrocodone for the treatment of chronic pain. (Tr. 907:15-908:7.) Dr. Rauck testified that, while he still writes Schedule II prescriptions, "I many times wish I didn't write as much as I even do." (Tr. 926:14-18.) Dr. Rauck testified that "[w]e certainly have patients though that either pain condition has required the Schedule IIs or we cannot get them to transition over." (Tr. 908:18-20.)

263. Buprenorphine is currently classified as a Schedule III opioid rather than Schedule II. However, for the treatment of chronic pain patients with opioids, there is no relevant difference between the two classifications because in either case, current regulatory standards, current standards of care, and the patient's best

interest impose a duty to see patients face to face on a recurrent basis. (Tr. 488:20-490:8.)

264. According to Endo, the DEA scheduling of Belbuca® ranked among the least relevant factors in terms of driving prescription behavior. (Tr. 466:16-467:10; DTX-043-0001.)

265. The adverse events for Belbuca® are very typical for an opioid. (Tr. 501:25-503:13.)

266. The characteristics of Belbuca® with respect to respiratory depression and the ceiling effect were not surprising. (Tr. 501:16-20.)

267. Dr. Fine is aware of no examples of industry praise from doctors that were not being paid by BDSI. (Tr. 511:3-6.)

VI. CLAIMS 3, 4, 5, AND 10 OF THE '866 AND CLAIMS 8 AND 20 OF THE '843 PATENT ARE ANTICIPATED

268. Vasisht I discloses all of the elements of claims 3-5 and 10 of the '866 patent, and claims 8 and 20 of the '843 patent. (D.I. 249 at 3; Tr. 232:2-232:13; 238:4-246:15; DDX3.36-DDX3.38)

269. Paragraph [0063] of U.S. Application No. 11/817,915 (the U.S. National phase based on Vasisht I, filed January 21, 2010) discloses the following values and ranges for the pH of the polymeric diffusion environment for use with buprenorphine: (a) between about 4.0 and about 7.5; (b) about 6.0; (c) about 5.5 to about 6.5; (d) between about 6.0 and 6.5; (e) about 7.25; (f) between about 7.0 and

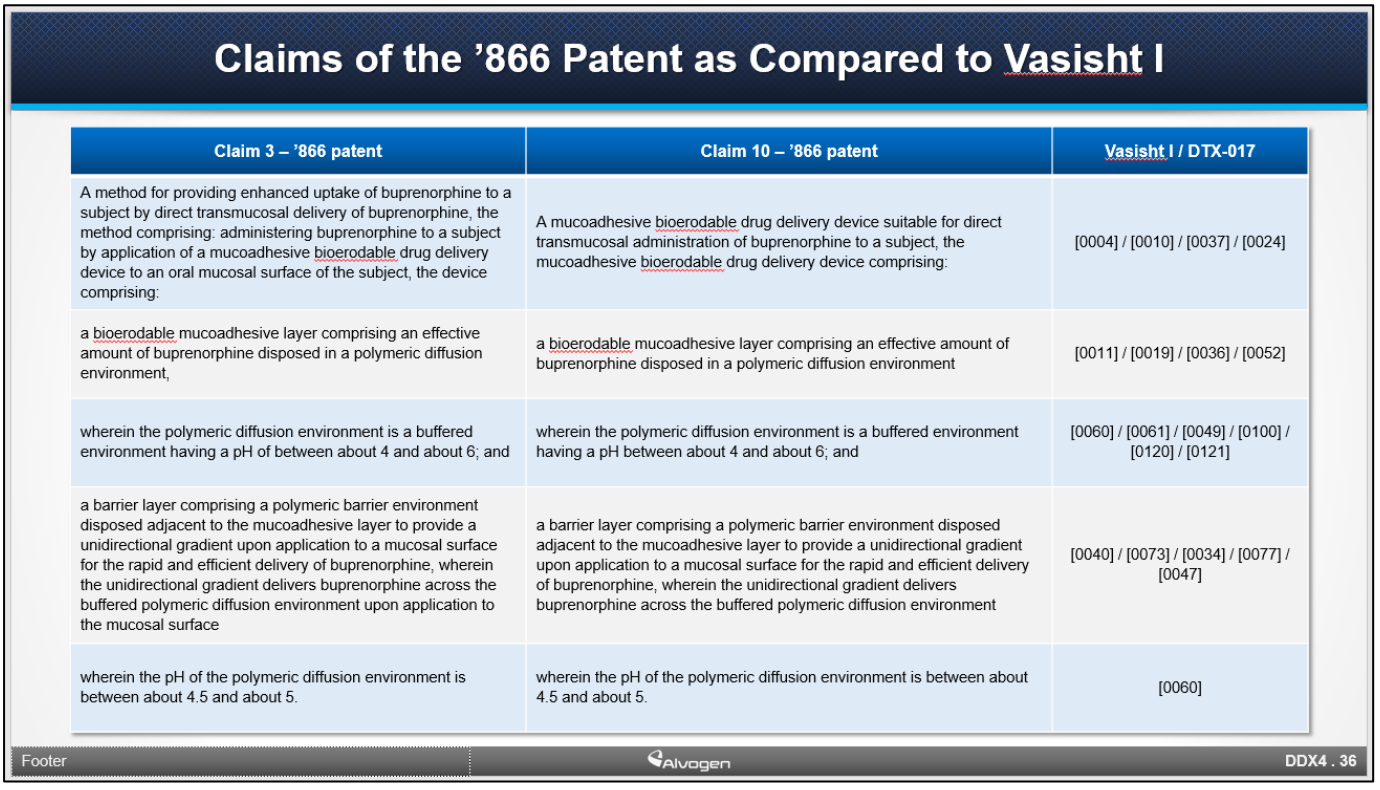
7.5; and (d) between about 7.25 and 7.5. (DTX-017 at [0063].) Dr. Michniak-Kohn testified that none of these values or ranges would suggest to a POSA that the patents disclose a pH between about 4 and about 6, between about 4.5 and 5.5 or between about 4.5 and 5 as recited in the claims. (DTX-206-0011 at [0063], Tr. 233:12-234:9.)

270. The last sentence of paragraph [0063] of the '915 application states "[i]n other embodiments, the pH of the device may be about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0 or 7.5, or any incremental value thereof." Dr. Michniak-Kohn testified that a POSA would not have understood this sentence to refer to the pH of the polymeric diffusion environment; rather a POSA would have understood it to refer to the pH of the pharmaceutical dosage form ("the device" in the parlance of the asserted claims) as whole. (DTX-206-0011 at [0063], Tr. 235:13-238:3.)

271. "The device" is a term that appears in all of the asserted claims of the '866 and '843 patents and is used repeatedly in the specification of the '915 application, e.g., in the Abstract, paragraph [0004] of the Brief Summary of the Invention and in paragraph [0091] of the Detailed Description of the Invention. In each case, the term "the device" refers to the entire pharmaceutical dosage form and is distinct from the "polymeric diffusion environment" which comprises but one element of "the device." (DTX-206 at Abstract, [0004], [0091].)

272. The Abstract and ¶[0020] of Provisional Application 60/832,726 (to which the '915 application claims priority) is entirely consistent with that of the '915 application. The Abstract states that the pH of the mucoadhesive layer is between about 4 and about 7.5 and ¶[0020] only mentions the pH of "the device." (JTX-238-0009 at Abstract, ¶[0020].)

273. The demonstrative below, admitted into evidence (*see* Tr. 245:20-246:17) summarizes claims 3 and 10 of the '866 patent as compared to Vasisht I.

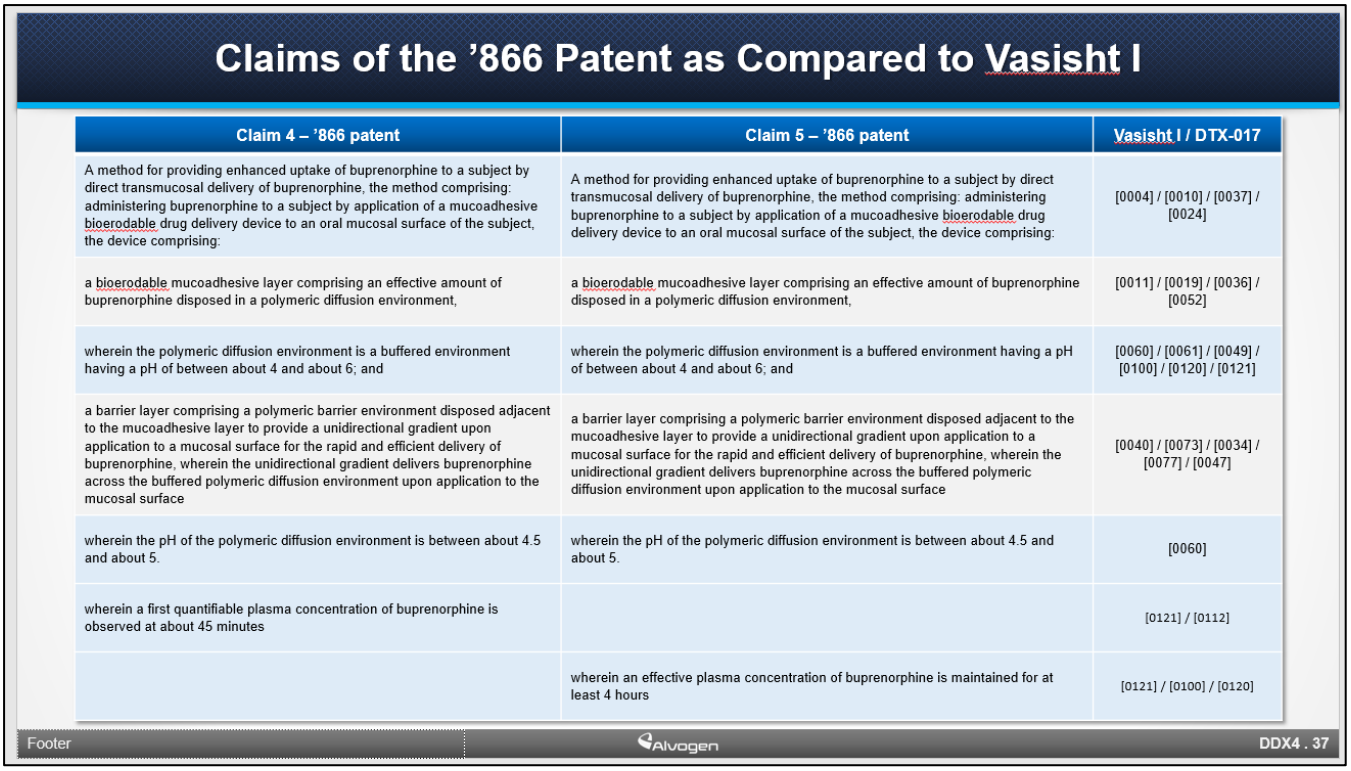


Claims of the '866 Patent as Compared to Vasisht I

Claim 3 – '866 patent	Claim 10 – '866 patent	Vasisht I / DTX-017
A method for providing enhanced uptake of buprenorphine to a subject by direct transmucosal delivery of buprenorphine, the method comprising: administering buprenorphine to a subject by application of a mucoadhesive bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising:	A mucoadhesive bioerodable drug delivery device suitable for direct transmucosal administration of buprenorphine to a subject, the mucoadhesive bioerodable drug delivery device comprising:	[0004] / [0010] / [0037] / [0024]
a bioerodable mucoadhesive layer comprising an effective amount of buprenorphine disposed in a polymeric diffusion environment,	a bioerodable mucoadhesive layer comprising an effective amount of buprenorphine disposed in a polymeric diffusion environment	[0011] / [0019] / [0036] / [0052]
wherein the polymeric diffusion environment is a buffered environment having a pH of between about 4 and about 6; and	wherein the polymeric diffusion environment is a buffered environment having a pH between about 4 and about 6; and	[0060] / [0061] / [0049] / [0100] / [0120] / [0121]
a barrier layer comprising a polymeric barrier environment disposed adjacent to the mucoadhesive layer to provide a unidirectional gradient upon application to a mucosal surface for the rapid and efficient delivery of buprenorphine, wherein the unidirectional gradient delivers buprenorphine across the buffered polymeric diffusion environment upon application to the mucosal surface	a barrier layer comprising a polymeric barrier environment disposed adjacent to the mucoadhesive layer to provide a unidirectional gradient upon application to a mucosal surface for the rapid and efficient delivery of buprenorphine, wherein the unidirectional gradient delivers buprenorphine across the buffered polymeric diffusion environment	[0040] / [0073] / [0034] / [0077] / [0047]
wherein the pH of the polymeric diffusion environment is between about 4.5 and about 5.	wherein the pH of the polymeric diffusion environment is between about 4.5 and about 5.	[0060]

Footer Alvogen DDX4 . 36

274. The demonstrative below, admitted into evidence (*see* Tr. 245:20-246:17), summarizes claims 4 and 5 of the '866 patent as compared to Vasisht.



Claims of the ’866 Patent as Compared to Vasisht I

Claim 4 – ’866 patent	Claim 5 – ’866 patent	Vasisht I / DTX-017
A method for providing enhanced uptake of buprenorphine to a subject by direct transmucosal delivery of buprenorphine, the method comprising: administering buprenorphine to a subject by application of a mucoadhesive bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising:	A method for providing enhanced uptake of buprenorphine to a subject by direct transmucosal delivery of buprenorphine, the method comprising: administering buprenorphine to a subject by application of a mucoadhesive bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising:	[0004] / [0010] / [0037] / [0024]
a bioerodable mucoadhesive layer comprising an effective amount of buprenorphine disposed in a polymeric diffusion environment,	a bioerodable mucoadhesive layer comprising an effective amount of buprenorphine disposed in a polymeric diffusion environment,	[0011] / [0019] / [0036] / [0052]
wherein the polymeric diffusion environment is a buffered environment having a pH of between about 4 and about 6; and	wherein the polymeric diffusion environment is a buffered environment having a pH of between about 4 and about 6; and	[0060] / [0061] / [0049] / [0100] / [0120] / [0121]
a barrier layer comprising a polymeric barrier environment disposed adjacent to the mucoadhesive layer to provide a unidirectional gradient upon application to a mucosal surface for the rapid and efficient delivery of buprenorphine, wherein the unidirectional gradient delivers buprenorphine across the buffered polymeric diffusion environment upon application to the mucosal surface	a barrier layer comprising a polymeric barrier environment disposed adjacent to the mucoadhesive layer to provide a unidirectional gradient upon application to a mucosal surface for the rapid and efficient delivery of buprenorphine, wherein the unidirectional gradient delivers buprenorphine across the buffered polymeric diffusion environment upon application to the mucosal surface	[0040] / [0073] / [0034] / [0077] / [0047]
wherein the pH of the polymeric diffusion environment is between about 4.5 and about 5.	wherein the pH of the polymeric diffusion environment is between about 4.5 and about 5.	[0060]
wherein a first quantifiable plasma concentration of buprenorphine is observed at about 45 minutes		[0121] / [0112]
	wherein an effective plasma concentration of buprenorphine is maintained for at least 4 hours	[0121] / [0100] / [0120]

Footer Alvogen DDX4 . 37

275. The demonstrative below, admitted into evidence (*see* Tr. 245:20-246:17), summarizes claims 8-20 of the ’843 patent as compared to Vasisht.

’843 Patent as Compared to Vasisht I

Claim 8 – ’843 patent	Claim 20 – ’843 patent	Vasisht I / DTX-017
A method for delivering buprenorphine to a human comprising: administering a mucoadhesive biodegradable drug delivery device for transmucosal delivery, the device comprising:	A device for delivering buprenorphine to a human, the device comprising:	[0004] / [0121] / [0022] / Fig. 3 [0010] / [0037] / [0098] / [0120]
a bioerodible mucoadhesive layer comprising buprenorphine disposed in a polymeric diffusion environment,	a bioerodible mucoadhesive layer comprising buprenorphine disposed in a polymeric diffusion environment	[0011] / [0019]
wherein the polymeric diffusion environment has a pH of between about 4 and about 7.5, and	wherein the polymeric diffusion environment has a pH of between about 4 and about 7.5; and	[0060]
a polymeric barrier environment disposed adjacent to the mucoadhesive layer, and wherein a unidirectional diffusion gradient of buprenorphine is provided upon application to a buccal surface.	a polymeric barrier environment disposed adjacent to the mucoadhesive layer, and wherein a unidirectional diffusion gradient of buprenorphine is provided upon application to a buccal surface of a human	[0040] / [0073] / [0034]
wherein the polymeric diffusion environment has a pH buffered to between about 4 to about 6.	wherein the polymeric diffusion environment has a pH buffered to between about 4 to about 6.	[0060] / [0061] / [0049] / [0100] / [0120] / [0121]

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CERTIFICATE OF COMPLIANCE

I hereby certify that the text of the foregoing document uses a 14-point Times New Roman typeface and contains 12,357 words as determined by the word count feature of Microsoft Word (excluding the caption, tables, signature block, and certifications).

Date: March 30, 2021

/s/ Steven H. Sklar
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